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NERVE METABOLISM

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One cannot fail, when considering the development of our knowledge and ideas concerning the activity of nerve, to be impressed with the validity of Ludwig's dictum, "Die Methode ist Alles." Until the end of last century practically all views attributed to nerve a completely passive rôle in the conduction of an impulse. Energy or substance entered one end of a cord or tube under the driving force of a stimulus and, having passed to the other end, itself or by replacement, emerged as a response. All the evidence available fostered such a theory, for a nerve could be kept active over long periods without fatiguing (83, 341, 94, 54), and it gave no manifestations of an active state except a feeble electric change, easily referable to simple physical effects (155). Helmholtz (335, 338), at the time of successfully measuring the heat production of muscle, failed in attempts to make similar measurements on nerve. A gas exchange had not been proved (338, p. 132 and 140), and the total of metabolic changes known, as indicted in Hermann's Handbuch of 1879 (vol. 2, no. 1, p. 136–142), was a dubious acid production of injury (226).

Attempts at intervals and by several experimenters to demonstrate such changes were for long entirely fruitless and might well have been

abandoned, had not two properties of nerve, established during this period—the all or nothing behavior during conduction (10, 387) and the refractoriness following (295, 472)—indicated that, after all, the nerve fibre must actively participate in the process of passing an impulse along it. The temporary burst of successes at the opening of this century—Baeyer's demonstration that nerves could be asphyxiated (34, 32), Thörner's further finding that activity hastened the asphyxia block (701), Thunberg's first crude but certain measure of a resting oxygen consumption (705), and the like—were negatived by the apparent absence of increased respiration (104) or heat production (344) during activity.

The final successful demonstration of the missing changes has been in each case primarily a matter of technical advance and greater sensitivity of method; and we now have seemingly conclusive evidence that the nerve impulse is a result of the activity of the nerve fibre, which obtains the energy for this propagation from familiar chemical reactions. I shall make no attempt to trace here in any detail the older contributions to the subject; the more so since, despite an exhaustive search of the literature, I have found little (within the scope of his article) not sufficiently covered by Winterstein in the new Handbuch (767).

In closing these introductory remarks, however, it is worth noting that a study of nerve metabolism should be of interest in several widely separated fields. On the one hand, it appears certain that many diseases of the nervous system—multiple sclerosis, combined cord degenerations, probably epilepsy, several of the insanities, including Korsakow's "wet brain," etc.—are primarily metabolic in character, rather than anatomic, and it seems a sane hope that their solution will be reached by way of metabolic studies. (See e.g., 758.) Similarly with fibre degenerations after trauma, drugs, and the like. On the other hand, the nerve cell and fibre afford perhaps the ideal case of a specialized cell able to perform one of the primary activities of protoplasm superlatively well, to the practical exclusion of all others. Because of this unitary behavior, and our ability to call forth its normal function in a quantitatively controlled manner, it offers great opportunity for the study of many fundamental problems of cell physiology. Certainly our concepts of cell membranes, polarization, and the like, which apply to all cells, were built in large part upon the findings in nerve.

Since the great bulk of investigation has been upon the medullated frog sciatic, this will occupy the body of the present review. Other myelinated nerves (e.g., mammalian) and non-medullated nerves (sym-

pathetic, invertebrate) will also briefly be considered; and some of the more striking metabolic data on end organs and nerve cells (ganglia, central nervous system, retina) included.

I. Histology—structural and chemical. A. *Influence of the Perineureum and Non-Neural Elements.* The ordinary green frog sciatic (R. pipiens) can be dissected from the spinal foramina, mainly 8–9 roots, to below the knee joint, as peroneal and tibial; and a length of 7–8 cm. and weight of about 35 mgm. is so obtained in fair sized specimens. Some 3000–4000 myelinated fibres are present (159, 160, 161) and, if Ranson's data on the mammal (616) may be applied, about twice as many non-myelinated. Surrounding the lot is a nerve sheath, or perineureum, from which fibrous trabeculae penetrate among the axones, separating them into fascicles, and even enveloping individual ones in a "sheath of Henle" (514).

This tissue, though not directly concerned with the function of nerve, may seriously affect *in vitro* studies in several ways. It affords a marked barrier to the passage of substances and introduces an extraneous polarizable resistance into the path of currents. Thus narcosis proceeds most rapidly at the level of branches (391, 621), where also mechanical injury is most easily inflicted, and a simple longitudinal slitting of the outer sheath may hasten the action of externally applied reagents by twenty times (195). There is an important difference between the common European frogs (temporaria especially) and the American in that the sheath is much finer in the former. The thick sheath on the bull-frog nerve is practically absent on its spinal roots (187). These relations probably account for many observed differences, such as the partial recovery of axphyxiated temporaria nerve obtained with oxygen-free Ringer (296, 127), and the non-recovery of pipiens until after the sheath is split (257, 195). The distorting effect of the sheath on stimulating or action currents has often been emphasized (685, 165, 75, 72, 73, 285, 475, 571).

A further complication due to connective tissue (including blood vessels and interstitial tissue as well as the fibrous layers; and possibly the neurilemma belongs here) appears in metabolic studies. As will be seen, the active metabolism of nerve is rather different, in kind as well as in amount, from that of resting nerve; and the latter must depend to some unknown extent on non-neural elements. Also when expressing changes, especially of activity, in quantitative units per unit mass of tissue, the true axone reactions are diluted by reckoning in non-nervous substance as well. Parker (588) has estimated that axones occupy 50

per cent of the nerve mass in the dogfish lateral line nerve; Ellison (173) found that axones occupied 37 per cent of the horse median, and of this only one-fourth was axis cylinder; and Netter (567), from diffusion experiments, estimated that only one-third of a frog sciatic was connective tissue. The probably wide limits of variability, both in individuals and in species, must be ascertained before these figures can be freely utilized. Also non-medullated fibres were not included in these estimates but, by analogy with invertebrate nerve (310, 700, 586, 538, 112), they probably have an intense metabolism. (But see 114.) This might even offset the diluting effect of fibrous tissue on the resting values, while further displacing those of activity; for these fibres are not stimulated by ordinary "maximal" induction shocks. It is especially misleading, on similar grounds, to express the metabolism of activity simply as a percentgage of that during rest. In the central nervous system the problem is far more acute, for hereglia and other non-neural elements constitute a great fraction of the total bulk. Parker (584) states that the volume of ganglion cells in the human cerebrum, for example, is 1 cu. in, which is about 1 per cent of the total; and, if only these enter into activity, their increased metabolism can in no reasonable way be represented by reference to the resting level. (Berger, 55, estimates 5.5 billion cells in 530 cc. of grey cortex, and Dahlberg, 133, finds 53 per cent of the cerebrum is grey. If the total cells are to occupy 1 per cent of the volume, about 13 cc., the average radius of each must be 17 μ. This may be a fair average, though many are much larger. Five billion pyramidal cells, 454, for example, would occupy the entire grey.)

B. *Fibre Types and Properties.* The 3000 odd myelinated fibres in the frog's sciatic vary widely among themselves as to diameter, thickness of myelin, etc., and seem to fall into two main functional groups: heavily medullated, somatic (A); and thinly medullated, visceral (B) (77). The larger of these, the heavily medullated or A group (189) contains three subgroups, α, β, γ. There is also a C group of non-medullated fibres. The anatomical grouping by fibre diameter paralles certain physiological criteria, such as threshold and conduction rate (436, 242, 243), and also other structural ones, such as internodal length (84, 17, 687, 329). Further, there is evidence (160) that each fibre is a prolonged cone, tapering peripherally, and a gradient of activity might be anticipated on this basis. (Though tapering has been denied, 435, 423, at least for motor fibres, 660, there is no doubt that fibres become smaller peripherally as a result of branching, 668, 159,

166.) Though posited by Child (117) and claimed by Tashiro (695, 696), it has not so far appeared in recent respiration studies (253, 589). In action potential studies with the cathode-ray oscillograph, however, Marshall and Gerard (505) have demonstrated a regular decrease of conduction rate (about 30 per cent) in the fast α fibres of the bullfrog nerve as the impulse passes peripherally. This change may be related to internodal length more closely than fibre diameter; but for a discussion of the significance of such structural-functional relations reference must be made to another place (265). A gradient in chemical composition has also been described, especially the PO_4 radicle increasing in concentration peripherally (627). Total phosphate shows a distinct gradient in green and bullfrog sciatics, being 15 to 35 per cent *less* in the distal than central third, according to preliminary observations in this laboratory, but the acid soluble fraction is constant (279).

The described fibre grouping is of more immediate concern for the present thesis in that quantitative differences in metabolic rate probably exist between the various groups (332, 257). Further, since rather sharp breaks in electrical threshold have been found, it is of importance to know for which groups a "maximal" stimulus is really so. In our own earlier experiments, all of the A groups, probably some B, and none of the C were stimulated. The regular Harvard coil with three volts in the primary (2MF condenser in parallel) and the secondary set at 12 cm. tilted at 60° from horizontal was a common set-up used.

C. *Neurofibrils.* The problem of neurofibrils must also largely be avoided. Although definitely present *intra vitam* in invertebrate nerve (86, 144) they have not been conclusively demonstrated in vertebrate; though they seem to appear during activity (601). Further, it is certainly an open question (600, 183) whether they serve a conducting (64), nutritive (441), or supporting (288) function. If fibrils are in fact the conducting element, metabolic changes, calculated per unit surface, would be considerably greater than if the axiolemma is the main reactive membrane. The considerable body of work devoted to a study of Bethe's "fibril acid," based on vital staining with toluidine blue under the action of a polarizing current, the whole nerve being subject to a variety of conditions (65, 663, 661, 67, 393, 643, 409), has thrown little light on nerve metabolism, though it is of interest in connection with membrane reactions. To the extent that staining properties may be relied on, the fibrils do contain some acid material; and this (or ions reacting with it) migrates under the influence of an electric current.

D. *Chemical Components.* The frog sciatic contains on the average 75 per cent water (115) and about one-sixth lipins (193). It is important, in considering the concentration of extractives in nerve fibres, to recall that the aqueous protoplasm (axis cylinder) occupies on the average only 25 (173), 40 (302) or 50 per cent (150, 76) of the nerve fibre volume, even neglecting the neurilemma and all connective elements. Thus, for example, the concentration of creatin in whole nerve is hardly one-third that in muscle (277, 278); but if this is largely limited to the axis cylinder, the concentration there might well be greater than in the muscle fibre. Alcock and Lynch (20) found 0.13 per cent of potassium in nerve but estimate 1.2 per cent in the axis cylinder. Data on the content in nerve of a number of substances are collected in table 1 (see also, 766, 657).

Histochemical studies have shown little or no potassium within the intact axis cylinder but considerable amounts about it at the nodes of Ranvier (482, 521), much like the "thorny collar" of Nageotte (559), and in the myelin. Following local injury, much potassium appears as a cobaltinitrite precipitate within the axis cylinder proper (487). This is presumably a consequence of liberation of these ions from a chemically or physically bound condition, though changes in penetration of the reagent are hard to exclude with certainty. More recent work (673, 555) gives no evidence, by out-diffusion experiments, of potassium existing in a wholly or partly bound fraction, nor of an unequal distribution in the nerve fibre (673). Chloride is also seen in greatest amount at the nodes of myelinated fibres, but here again entrance of the silver reagent may determine the local picture (483, 576). The myelin appears relatively chloride free and the axis cylinder richer than the cell body or surrounding fluid. Direct analyses of medullated and non-medullated nerves, however, indicate an equal distribution of chloride between axis cylinder and myelin (18).

A salt migration along the nerve during activity has been reported. Experiments on dog (418) and frog (627) sciatics indicated a shift of potassium and calcium ions from the central stimulated portion toward the peripheral end, that is, in the direction of travel of the nerve impulses. The concentrations in proximal, middle and distal regions were equal in resting nerves but unequal, in the manner indicated, after long tetanization. Phosphorus, on the contrary, is unequally distributed in resting nerves, the distal portion being richer; but during activity there is migration toward the proximal end, opposed to the direction of impulse travel (627). Although the analyses show great variability

TABLE 1

SUBSTANCE	NERVE	CONCENTRATION		OBSERVER	DATE	REFERENCE	REMARKS
		Wet weight	Dry weight				
		per cent	*per cent*				
Water	Frog, sciatic	74.6		Chang and Gerard	1931	115	Autumn frogs
	Dog, popliteal	69.7		Alcock and Lynch	1907	18	
	Dog, vagus	71		Gerard and McIntyre	1931	273	
	Cat, popliteal	67.3		Alcock and Lynch	1907	18	
	Cat, sciatic	65		Mott and Halliburton	1901	553	
	Rabbit, sciatic	66		May	1930	516	
	Beef, various	66		Abderhalden and Weil	1912	2	
	Lobster, claw	87.8		Chang	1931	112	
	Limulus, leg	83.5		Chang	1931	112	
Total ash	Beef, various	1.1	(3.2)*	Abderhalden and Weil	1912	2	
	Horse, median	1.0	(3.0)	Alcock and Lynch	1910	19	
	Cat, sciatic	1.0	(3.0)	Halliburton	1893	314	
S	Horse, median	0.04	(0.12)	Alcock and Lynch	1910	19	Total S = 0.12. Other value for ash
Na	Horse, median	0.45	(1.3)	Alcock and Lynch	1907	18	
K	Horse, median	0.13	(0.38)	Alcock and Lynch	1911	20	
	Frog, sciatic	0.2–0.8	(0.8–3.2)	Roeder	1930	627	
	Rabbit, sciatic	0.2–2.1	(0.7–7.1)	Simon and Szelöczey	1928	673	
	Horse, splenic	0.18	(0.7)	Alcock and Lynch	1911	20	
Ca	Frog, sciatic	0.4–1.5	(1.6–6.0)	Roeder	1930	627	
	Rabbit, sciatic	0.13–1.2	(0.4–4.1)	Simon and Szelöczey	1928	673	
Cl	Horse, median	0.27	(0.8)	Alcock and Lynch	1911	20	
	Cat, popliteal	0.23	(0.76)	Alcock and Lynch	1907	18	
	Horse, splenic	0.15	(0.6)	Alcock and Lynch	1911	20	

P	Horse, various	(0.2–0.3)	0.6–1.0	Dehere and Maurice	1909	142	Total
	Horse, various	(0.09–0.12)	0.3–0.4	Dehere and Maurice	1909	142	Lipoid
	Horse, various	(0.02)	0.06–0.07	Dehere and Maurice	1909	142	Nucleic
	Horse, various	(0.07–0.15)	0.25–0.5	Dehere and Maurice	1909	142	Inorganic, all lower values in older animals
	Cat, sciatic	(0.3+)	.1.1	Mott and Halliburton	1901	553	Total
	Rabbit, sciatic	(0.3+)	1.0–1.2	May	1930	516	Total
	Rabbit, sciatic	(0.19)	0.65	May	1930	516	Lipoid
	Horse, median	0.25	(0.74)	Alcock and Lynch	1910	19	Total
	Frog, sciatic	0.22	(0.9)	Hecker	1923	330	Total
	Frog, sciatic	0.03	(0.1)	Gerard and Wallen	1929	280	Acid soluble
	Frog, sciatic	0.41	(1.6)	Gerard and Wallen	1929	280	Total
	Frog, sciatic	0.35–1.4	(1.4–5.5)	Roeder	1930	627	Total
	Frog, sciatic	0.03	(0.12)	Gerard and Tupikow	1931	279	Acid soluble, autumn
	Frog, sciatic	0.05	(0.20)	Gerard and Tupikow	1931	279	Acid soluble, winter
	Frog, sciatic	0.26	(1.0)	Gerard and Tupikow	1931	279	Lipoid, winter
	Frog, sciatic	0.35	(1.4)	Gerard and Tupikow	1931	279	Total, winter
	Lobster, leg	0.05	(0.55)	Tang, Tang and Gerard	1932	693	Acid soluble
Lipoids	Human, sciatic	(15.2)	46	Falk	1908	193	Total
	Horse, various	(15–20)	43–60	Dehere and Maurice	1909	142	Total. High values in old animals
Phospholipin	Human, sciatic	(11.6)	34	Chevalier	1886	116	
	Human, sciatic	(2.4)	7	Falk	1908	193	
Cholesterol	Human, sciatic	(4.1)	12	Chevalier	1886	116	
	Human, sciatic	(4.1)	12	Falk	1908	193	
Cerebrosides	Human, sciatic	(3.7)	11	Chevalier	1886	116	
	Human, sciatic	(2.9)	8.5	Falk	1908	193	

TABLE 1—*Concluded*

SUBSTANCE	NERVE	CONCENTRATION		OBSERVER	DATE	REFERENCE	REMARKS
		Wet weight	Dry weight				
		per cent	*per cent*				
Carbohydrates							
Glycogen	Frog, sciatic	0.02–0.06	(0.08–0.24)	Gerard and Meyerhof	1927	275	
	Bullfrog, sciatic	0.02	(0.08)	Holmes, Gerard and Solomon	1930	368	
	Rabbit, sciatic	0.05–0.06	(0.17–0.2)	Holmes and Gerard	1929	367	
	Crab, leg	0.3–2.2	(1.9–14)	Holmes	1929	364	
"Lower sugars"	Frog, sciatic	0.03–0.18	(0.12–0.7)	Gerard and Meyerhof	1927	275	
	Bullfrog, sciatic	0.09	(0.35)	Holmes, Gerard and Solomon	1930	368	
	Rabbit, sciatic	0.03–0.07	(0.1–0.24)	Holmes and Gerard	1929	367	
	Crab, leg	0.22	(1.4)	Holmes	1929	364	
Lactic acid	Frog, sciatic	0.07–0.11+	(0.28–0.44)	Gerard and Meyerhof	1927	275	
	Bullfrog, sciatic	0.07	(0.3)	Holmes, Gerard and Solomon	1930	368	
	Rabbit, sciatic	0.05–0.11	(0.17–0.37)	Holmes and Gerard	1929	367	
	Crab, leg	0.10–0.23	(0.6–1.4)	Holmes	1929	364	
Sugars	Frog, sciatic	0.40–0.58	(1.6–2.3)	Winterstein and Hirschberg	1925	774	Ppted. by alcohol
Ammonia	Frog, sciatic	0.0025	(0.01)	Gerard and Meyerhof	1927	275	
	Frog, sciatic	0.004	(0.016)	Gerard and Wen	1929	281	
Creatin	Frog, sciatic	0.16 (0.1–0.23)	(0.6)	Gerard and Tupikow	1930	277	Marked seasonal variation
	Bullfrog, sciatic	0.14	(0.6+)	Gerard and Tupikow	1930	277	40 per cent as creatin —phosphate
	Dog, sciatic	0.14	(0.47)	Gerard and Tupikow	1930	277	
	Chicken, sciatic	0.11	(0.35)	Gerard and Tupikow	1931	279	

Protein	Frog, sciatic	(7)	27–30	Hirschberg and Winterstein	1919	358	Calc. from N value
	Frog, sciatic	(7)	19–38	Roeder	1930	627	
	Beef, various	(13)	38	Abderhalden and Weil	1912	2	
	Human, sciatic	(11)	37	Chevalier	1886	116	
	Cat, sciatic	(11)	29	Halliburton	1893	314	
Amino acids	Beef, various						
Arginine			Amino acid N in per cent of protein N decreases in order given from 3.5 to 1.5	Abderhalden and Weil	1912	2	Only 15 per cent of protein N recovered
Lysine							
Glutamic							
Alanine							
Leucine							
Tyrosine			Values decrease from 0.8 to 0.2				
Histidine							
Proline							
Serine							
Glycoll			Absent				

* Bracketed value estimated from other one.

and direct polarization of a frog sciatic did not result in potassium migration (49—due possibly to current flow being largely in free fluid between fibres and around the nerve sheath) these results, if confirmed, will be of considerable interest. It has been pointed out (513), from an entirely different approach, that the prevailing theory of nerve conduction does call for such a displacement of cations in one direction and anions in the other in a cumulative manner with repeated one-way transmission of impulses. Our own results on phosphate have so far been negative.

The enzymic activities of grey and white matter, and in some cases of peripheral nerve, have been studied histologically and chemically, especial attention having been devoted to oxidases as revealed by the Nadi reagent. The indo phenol oxidase has been often so demonstrated in cell bodies and dendrites and the considerable variation in the amount in various brain regions studied (722, 392, 162, 498, 500, 501, 497, 502, 429, 430, 367). It has also been found absent, microscopically, in the body of the axis cylinder, but only where and when this is covered by myelin (392, 498, 500, 429, 59). Since some reaction has been seen in the myelin itself (502), and ground, washed nerve does show an oxygen uptake with the Nadi reagent (367), it seems probable that failure to detect the oxidases in axones depends rather on lack of penetration of the reagents than on its absence. The amount present in nerve is, however, much less than in brain, possibly only $\frac{1}{25}$ as much (367). Further evidence, from the action of toxins (162), narcotics (162, 430) and strychnine (430), suggests a parallelism between the functional state and oxidase concentration in the cell bodies, as well as between respiration intensity and oxidase content of centers and peripheral nervous structures (367).

Among the enzymes reported in nervous tissues are: diastase (385, 690), lipase (385, 501, 690), lecithinase (esterase) (575, 715, 682, 353), glycerophosphatase (729), nuclease (690), glycolytic (690, 275, 367), glyoxalase (728), proteolytic (gelatinase) (385, 501, 690, 422), catalase (38), and oxido-reductase (460) fumarase (611), succinoxidase (612), and several dehydrases (707, 253, 365).

II. Resting metabolism. A. *In Oxygen.* 1. *Respiration.* a. *State of isolated nerve.* Gross information as to the magnitude of the resting metabolism is best obtained directly from the rate of energy degredation, or heat production, or indirectly (if dependent on aerobic processes) from the oxygen consumed. To the extent that an isolated nerve, composed largely of axones severed from their cell bodies, is in

a steady state, all finer intermediate reactions remain in equilibrium so long as oxygen and food stuff are ample. That such an equilibrium—undisturbed on the one hand by degenerative changes or on the other by bacterial action—does maintain for many hours, or days at lower temperature, is demonstrated by the constancy of respiration over such a period and the absence of change in condition of intermediate substances. This statement is subject to minor qualifications.

For an hour or more after dissection the respiration of nerve is above the later constant rate (585, 587, 253). Since cutting or grinding a nerve gives a brief increase in oxygen usage (253), this early excess may well be an aftermath of the dissection; but it may also represent, as appears to be the case for uninjured muscle (528), a remnant of a higher *in vivo* respiration, which is normally kept up by hormonal or nervous influences. Sugar disappears from frog nerve at a constant rate, though from rabbit nerve at a decreasing one (367, 368). Resting nerve kept in oxygen also shows a progressive increase in acid-soluble phosphate (280), which may mean an oxidation of phospholipins; and of ammonia, possibly from protein sources (697, 773, 275). The production of lactic acid during oxygen deprivation and with an adequate glucose supply also remains constant for long periods (275). The respiration of rabbit nerve, contrary to that of frog, falls almost from the start (367, 260, 666) but can be maintained at full value by the addition of glucose or galactose (667). Dog nerves in serum also maintain a roughly constant respiration for some time (273, 114). There are good grounds, therefore, for regarding the resting isolated nerve, supplied with adequate foodstuff and oxygen, as maintaining a state of approximate equilibrium not far different from that in the body.

b. *Oxygen supply.* The supply of oxygen to any tissue mass deprived of its circulation depends on diffusion from the surrounding medium. Whether or not this be adequate depends on the external partial pressure (concentration), the shape and size of the tissue and its rate of oxygen usage, and on the diffusion constant of the gas. Fenn (201) and Gerard (253) have developed in different ways an equation expressing these relations for a cylinder, analogous to Warburg's expression for a flat slice (737). Recently Hill (348) has formulated a more complete set of equations, covering, among other things, the non-equilibrium state, and Gerard (263) has presented formulae, more particularly for a sphere, which eliminate the assumptions necessary for the more simple expression, the assumption that the oxygen consumption of any one

region is independent of the local concentration being especially dangerous. Using this and minor simplifications, the equation for a cylinder reads

$$C_o = \frac{Ar_o^2}{6D}$$

where C_o is the minimum external oxygen concentration for full penetration; A is respiratory rate; r_o, surface radius and D, diffusion coefficient. When all values are expressed in centimeter, minute, atmosphere units and Krogh's (424) diffusion constant through fascia applied, the critical oxygen concentration in a gas to just supply an average temporaria nerve at rest at 15°C. is calculated at 1 per cent. (Fenn's, 203, constant for nerve — 1.8 × CO_2 value — is 8.5 in units where Krogh's for connective tissue is 37, or hardly one-fourth as great. This would increase C_o. There is a real possibility that the true constant for passage into, rather than between cells is lower still (692).) Experiment demonstrated a constant oxygen consumption as its concentration was lowered to 1.25 per cent and a considerable fall at the next lower value of 0.5 per cent (253). The problem is being followed with more exact methods in an attempt to determine to what extent the main assumption mentioned, that consumption is independent of local oxygen pressure, is valid; since the curve of oxygen consumption for a local region, that is, after diffusion has been allowed for, must be a significant index to the underlying mechanisms. For R. pipiens nerve at 20°C., and especially during activity, a gas mixture would require 2.5–4 per cent oxygen for full penetration. Since experiments with carbon monoxide require low oxygen and have often been performed with 2 per cent of this gas, some asphyxia may have occurred. Mixtures of nitrogen or hydrogen with oxygen have, in fact, shown a slight depression with 2 per cent of the gas, but none with 3 per cent (115). The thicker mammalian nerves at body temperature require still higher oxygen concentrations, and air must be replaced by oxygen to insure full penetration—even the pure gas being below the optimum for very thick nerves or if exposure is not free.

c. *Respiratory exchange.* Subject to these considerations, the resting metabolism can be obtained from the oxygen consumption, the carbon dioxide production (for a given R.Q.), or the heat liberation. This latter may be approximately translated into oxygen even when the fuel burned is unknown, since the ratio of heat produced (gm. cal.) to oxygen consumed (mgm.) varies by only 7 per cent between protein (3.2) and

carbohydrate (3.4–3.5) (53). Table 2 summarizes the more pertinent values of resting respiration, expressed as oxygen consumed. It is satisfactory to note that Fenn's latest results (some corrected for drying, 204, 201) on the American green frog sciatic obtained by a volumetric method and Gerard's (260) by a manometric one are in full agreement. The marked differences between the various frog species are, therefore, real and not methodical errors.

d. *Seasonal, ion and other influences.* The amphibian, though convenient in so many ways for experimentation, offers a complication in its marked seasonal variations in nutritional state and metabolism. There is seen a marked increase in respiration at the breeding season, affecting nerve (253), muscle (528), and probably the whole animal. A seasonal variation in nerve oxidizing reserve has been found (205). Even more striking variations are seen in the creatin content over a period of months (277). Further important variables are length of captivity, temperature and other conditions during this time, size (small nerves have a higher respiration per unit weight than large, 253, 199), nutrition, disease and the like. Early spring frogs regularly show great hydration and tissue edema, red-leg is common, etc. Pigmentation of the nerves also varies widely, the same batch of frogs yielding practically white and deeply yellow ones. (This may be the carotin pigment reported by Monaghan and Schmitt, 548, and may also be at the basis of a pink color appearing in nerves kept moist over chloroform for some time—266.) It is hardly surprising, in the absence of any standard animal, that nerves from different frogs in the same batch may differ by over 100 per cent in their respiration. Right and left nerves from the same animal, on the other hand, may be depended on to agree within 10 per cent; and it is necessary, if recourse to the statistical method is to be avoided, to pair off control and experimental nerves. The same holds for other metabolic studies.

The medium in which frog nerve is kept during study has no influence, over wide limits, on its respiration (260). This is alike in moist air, oxygen, Ringer, or isotonic NaCl, despite the stimulating action attributed to the latter. (But see below.) The phenomenon of reversible inexcitability, seen in muscles prior to soaking in Ringer (157, 374) and associated with increased oxygen consumption (206) does not appear in nerve. Addition to sodium chloride of 10 per cent calcium, potassium or magnesium chlorides, or 5 per cent of any two, has no effect, though pure or richer solutions of any one depress (260, 114; see also 650 on potassium; also compare 206 on muscle and 406). Substances lowering

TABLE 2

Resting oxygen consumption

ANIMAL	NERVE	SEASON	TEMPERATURE	OXYGEN CONSUMPTION		OBSERVER	DATE	REFERENCE	METHOD	REMARKS
				Average	Extremes					
				cmm. per gram and hour	*cmm. per gram and hour*					
Frog:										
Temporaria	Sciatic	Winter	14.6°	23.0	17–27	Gerard	1927	253	O_2—manom.	
			15.2	14.5	12.4–18.9	Meyerhof and Schmitt	1929	537	O_2—manom.	
		Spring	22	65	50–80	Adam	1921	7	O_2—manom.	
			19	71		Winterstein and Hirschberg	1926	766	O_2—volum.	
			14.6	28		Gerard	1927	253	O_2—manom.	
			15.0	26.0		Schmitt	1929	650	O_2—manom.	
Esculenta	Sciatic	Winter	16	22		Thunberg	1904	705	O_2—volum.	
			?	44		Buytendijk	1910	104–105	O_2—Winkler	
			19–24	63	42–83	Haberlandt	1911	310	O_2—manom.	
			14	14–15		Gerard	1927	255	Heat	Calc. for oxidation of carbohydrate (14) or fat (15)
			14.6	16	11–21	Gerard	1927	253	O_2—manom.	
		Spring	14.6	21		Gerard	1927	253	O_2—manom.	

Pipiens	**Sciatic**		**20**	**210**		Tashiro	1913	694	CO_2—Ca ppt.	Calc. for R.Q. = 0.8
			17–22	205		Riggs	1919	624	CO_2—Ca ppt.	Falls to 95 in half an hour. Calc. for R.Q. = 0.8
			19	235		Niwa	1919	574	CO_2—Ca ppt.	Cocaine stimulates to value of active respiration. Calculated for R.Q. = 0.8
			?	2,200		Sheaff	1922	665	O_2—chem.	
			22	55		Fenn	1927	201	O_2—volum.	Corrected for temp. and drying (= 20 per cent reduction)
			20	42		Fenn	1928	204	O_2—volum.	Corrected for temp. and drying (= 20 per cent reduction)
			21.5	42	20–80	Gerard	1930	260	O_2—manom.	
		Winter	22	37	19–62	Fenn	1930	205	O_2—volum.	Calc. from tables, corrected for temp.
		Summer	22	56	28–112	Fenn	1930	205	O_2—volum.	Calc. from tables, corrected for temp.
Clamitans	**Sciatic**		22	120	100–140	Parker	1928	589	CO_2—color.	Calc. for R.Q. = 0.8
Catesbiana	**Sciatic**		21	29		Gerard	1930	260	O_2—manom.	
Grylio	**Sciatic**		22	130	120–150	Parker	1928	589	CO_2—color.	Calc. for R.Q. = 0.8

TABLE 2—*Continued*

ANIMAL	NERVE	SEASON	TEMPERATURE	OXYGEN CONSUMPTION		OBSERVER	DATE	REFERENCE	METHOD	REMARKS
				Average	Extremes					
				cmm. per gram and hour	*cmm. per gram and hour*					
Dogfish:										
Smooth	Lateral line		22	74	55–98	Parker	1928	589	CO_2—color.	Calc. for R.Q. = 0.8
			22	75		Fenn	1927	199	O_2—volum.	Corrected for temp. Rises rapidly after 8–10 hrs.
			22	62		Gerard, etc.	1930	606	O_2—manom.	
			22	64+		Root	1931	630	O_2—Henderson-Haldane	Rises rapidly after 8–10 hrs. Includes some spiny
					25–157					
Spiny	Lateral line		22	30		Root	1931	631a	O_2—Henderson-Haldane	
Fish:										
Gadus Morrhua	Trigeminal		?	90	70–120	Buytendijk	1910	104–105	O_2—Winkler	
Electric ray	Electric		20	15		Gerard, etc.	1930	606	O_2—manom.	
Snake:										
(Drymarchon)	Vagus		22	90	65–120	Parker	1929	590	CO_2—color.	Calc. for R.Q. = 0.8

Rabbit	Sciatic		16	34		Thunberg	1904	705	O_2—volum.	
	and		37	280		Gerard	1930	260	O_2—manom.	320 at first; falls with time
	brachial		37	290	200–350	Sherif	1930	666	O_2—manom.	2nd hour = 235
Dog	Sciatic		38	120		Gerard	1930	260	O_2—manom.	Degen. for 1 week has no effect. Barbital animals
			22	30		Gerard	1930	260	O_2—manom.	Degen. for 1 week has no effect. Barbital animals
	Vagus		38	180	135–195	Gerard and McIntyre	1931	273	O_2—manom.	Prolonged thyroid feeding raises resp. by 25 per cent
	Vagus		38	190		Chang and Gerard	1932	114	O_2—manom.	Falls slowly in serum or saline. Higher at start and rapid rise after
	Phrenic		38	140		Chang, Gerard and Shaffer	1932	114	O_2—manom.	Falls 4 hours in saline
	Sympathetic		38	210		Chang	1932	114	O_2—manom.	Falls
Lobster	Ventral cord		23	185	falls to 60	Parker	1925	586	CO_2—color.	Corrected by 1928 results. Calc. for R.Q. = 0.8
			24	123	107–139	Chang	1931	112	O_2—manom.	Falls very little with time
	Leg		24	81	48–122	Chang	1931	112	O_2—manom.	Falls very little with time

TABLE 2—*Concluded*

ANIMAL	NERVE	SEASON	TEMPERATURE	OXYGEN CONSUMPTION		OBSERVER	DATE	REFERENCE	METHOD	REMARKS
				Average	Extremes					
				cmm. per gram and hour	*cmm. per gram and hour*					
Limulus	Heart gang.		23	130	175♂, small 90♀, large	Tashiro and Adams	1914	700	CO_2—Ca ppt.	Calc. for R.Q. = 0.8
			25	114	30–217	Dann and Gardner	1930	137	O_2—manom.	
	Claw		23	100		Tashiro and Adams	1914	700	CO_2—Ca ppt.	Calc. for R.Q. = 0.8
			24	82		Chang	1931	112	O_2—manom.	
	Optic		23	100		Tashiro and Adams	1914	700	CO_2—Ca ppt.	Calc. for R.Q. = 0.8
Spider crab	Leg		16	120		Meyerhof and Schultz	1929	538	O_2—manom.	
			22	125		Gerard, etc.	1930	606	O_2—manom.	
	Claw		15	255		Tashiro	1913	694	CO_2—Ca ppt.	Calc. for R.Q. = 0.8
			20	300		Tashiro and Adams	1914	698	CO_2—Ca ppt.	Calc. for R.Q. = 0.8
Octopus	Mantel		16	60		Meyerhof and Schultz	1929	538	O_2—manom.	

ionic calcium—oxalate, citrate, tartrate—on the contrary, lead to marked increases in respiration (115, 114). Sodium sulphate also accelerates carbon dioxide production (624) and oxygen consumption (114). Recent experiments with several types of dog nerve (114) regularly showed differences in respiration depending on the medium. In serum, the rate fell slowly over eight or more hours. In saline or Ringer buffered with phosphate the initial values were higher and the fall more rapid for three or four hours, after which a marked increase occurred, often to more than double the initial rate. This did not occur with unbuffered Ringer, and did occur in decalcified serum. Adding calcium ion removers to saline led to similar increases at once, and the effectiveness of phosphate, sulphate, fluoride, oxalate and citrate was in the order of their calcium removing ability. Experiments on frog nerve at 37° yielded similar results and a sharp rise of oxygen consumption after 6–7 hours in saline but a slow fall in unbuffered Ringer. It seems clear that the absence of calcium from the medium leads in some hours to a rise in respiration. At 20° the effect does not appear in 20 hours, at 37° in 3 to 7, but when calcium is removed by chemical reaction from the nerve itself, the rise is immediate.

It must be cautioned that some of these and the following observations were made on nerves with intact sheath and therefore partially protected; since many positive effects were obtained, however, this may not have been important. Also, where the sheath was split, the same effects were obtained, but more rapidly. No influence is exerted by pH between 6 and 9, although in the central nervous system respiration seems to parallel alkalinity (298, 343). Solutions up to four times isotonic have little effect; hypotonic ones depress increasingly with dilution, to a value $\frac{1}{3}$ normal in water. Phosphate increases respiration 15 per cent (or more, 656); bicarbonate is ineffective. Carbon dioxide above 5 per cent concentration depresses oxygen usage to about 40 per cent at 20 per cent carbon dioxide or over (630). Creatin has no effect (115); thyroid feeding increases it a fourth or more (273). Chloroform depresses after an initial increase (253), chloral hydrate and urethane at once, but morphine not at all, as used. The depression of respiration by the different narcotics far from parallels their ability to block conduction. Sodium lactate, in contrast to its action on muscle (532), does not affect nerve,—which is in harmony with the inability of this tissue to oxidize it (275, 367); nor do glucose, insulin or both (with an exceptional marked increase, 260, or depression with stronger glucose solutions, 114. Compare 48 on increased vagus irritability at once

after insulin injection). Rabbit nerve oxidations are maintained by glucose and galactose, accelerated by 0.1 per cent caffeine, and depressed by cocaine, urethane, novocaine, quinine, eucupinotoxin and 1 per cent caffeine (666). A reported stimulation of frog nerve by cocaine (574) has been questioned (666).

The temperature coefficient of the resting oxygen consumption is 2.2 for frog sciatic between 15° and 25° (253) (also to 37°), 1.8 for lobster claw nerve (112). The influence of dyes and of respiratory poisons will be considered separately.

2. *Respiratory quotient.* Although oxygen consumption is measured, in a sufficiently sensitive volumetric or manometric apparatus, with little complication, the determination of carbon dioxide produced is subject to several sources of error (fully discussed by Richardson, 622). An excessive amount may be given off from tissue or medium due to liberation from bicarbonate by stronger acids; or if acid disappears, a similar retention must result. These effects are directly utilized to measure lactic acid formation or removal, phosphocreatin breakdown, etc., by having the nerve in a bicarbonate containing medium with carbon dioxide present in the gas phase and alkali omitted; but when the true respiratory carbon dioxide is desired, these must be avoided or corrected for.

The simplest method for determining R.Q., comparison of gas change when alkali is present to absorb carbon dioxide (giving oxygen taken up) and when it is absent (giving oxygen less carbon dioxide liberated), must be checked in various ways. The change in bound carbon dioxide can be controlled by using companion nerves and pouring strong acid on one at the start, on the other at the close of the run. The carbon dioxide liberated is then corrected for any difference. By this method Gerard (253) obtained an average R.Q. of 0.77 at rest. Carbon dioxide here is determined by the difference between two readings (oxygen alone, oxygen minus carbon dioxide) on separate nerves. By the use of Warburg's differential solubility method (738), essentially the same figure was obtained—in this case carbon dioxide and oxygen being determined for the same nerve. For small readings the results may, however, show a wide scatter. To gain the greater assurance of separately determining oxygen and carbon dioxide on the same sample, Meyerhof and Schmitt (537) developed the method of absorbing in baryta the carbon dioxide liberated during a run, thus obtaining oxygen consumed, and later pouring citric acid over the nerve and baryta, so liberating and measuring all carbon dioxide present. Initially bound carbon dioxide is determined as in the previous work by pouring acid on the companion

nerves at the start of a run, and this is subtracted from the total. The average R.Q. of all these experiments was identical with that found by Gerard, but the authors regard as best a group of four, giving an R.Q. of 0.7.

Fenn (202) utilized another approach for determining the R.Q. The liberated carbon dioxide was taken up by a barium hydroxide solution of known conductivity and the decrease of conductivity, resulting from barium carbonate precipitation, determined at intervals by tipping the solution into an arm of the chamber supplied with electrodes. The change in each gas was thus directly measured on the same tissue sample, and R.Q. values of about 0.8–0.9 were obtained. (Values were considerably higher, 1.5 to 2.0, for some hours after dissection. This is in harmony with the extra burst of carbon dioxide for some time after dissection, 587.) In most of his experiments, however, he utilized the presence or absence of alkali method and obtained R.Q. values on the whole below 0.8. These he regarded as low because of another source of error.

Aside from fixed acid formation or removal, the carbon dioxide content of a tissue must vary with the external partial pressure of the gas along some dissociation curve typical for it. When alkali is omitted from a chamber and carbon dioxide accumulated, the bound carbon dioxide should then increase; and, some of the carbon dioxide formed being retained, a falsely low R.Q. would result. Fenn actually determined this curve for nerve (203) and showed that as the carbon dioxide tension rises from zero to 40 mm. about 10 vol. per cent becomes bound. When his observed R.Q. values were corrected with the aid of these data (or when working in the flatter region of the dissociation curve, by starting with 5–20 per cent carbon dioxide in the oxygen), they gave an average resting value of 0.97. (Root, 631a, finds in dogfish nerve a very different dissociation curve. The carbon dioxide bound is about linear with carbon dioxide pressure up to 50 per cent of the gas. There follows a plateau to 90 per cent and another increase in bound gas at this concentration. To what extent this curve depends on the large urea content of elasmobranch tissues has not been worked out. Root also obtained an apparent R.Q. of 0.82, 631.)

These high values are in disagreement with those of Gerard, and a further difficulty exists in that Gerard, directly measuring bound nerve carbon dioxide, did not find the increase, during a run with no alkali, to be anticipated from Fenn's curves. Also, the R.Q. measured in the presence of 5 per cent carbon dioxide actually averaged below that in

oxygen alone, although retention should have been much greater in the latter case. The divergence is probably due to the preliminary handling of the nerves. Fenn used them as dissected with no intermediate contact with liquids, whereas my nerves were put in a Ringer free from phosphate and carbonate when dissected and remained, often, for over an hour before being run in the manometers in fresh Ringer. In the second case, considerable out-diffusion of buffer probably eliminated most of the carbon dioxide combining capacity. That such a progressive loss of capacity does occur is seen from the curves of Meyerhof and Schmitt (537).

It is of value to have the resting R.Q. to translate quantitative determinations based on oxygen or carbon dioxide measurements into one another, as done above. It may also be used in the traditional manner to determine the kinds of foodstuffs burned. This latter, however, must be done with considerable reserve, because of uncertainty not only of measurement but also of interpretation. A given R.Q. may be the resultant of a great number of combinations of unit reactions, and direct chemical attack on these has not enhanced confidence in one's ability to say which particular one it represents. For example, the R.Q. of the active metabolism of nerve is about 0.2 higher than that of the resting, but direct analysis shows considerable sugar used at rest and no further change during conduction. It is interesting that glucose addition does not affect the R.Q. of nerve any more than the total respiration, though exerting a marked influence on glycolysis (275).

3. *Intermediate processes.* a. *Carbohydrate.* At rest in oxygen the "free carbohydrate" content of nerve decreases, while the glycogen (and lactic acid) remains constant. Hexose phosphate also probably is unchanged or, if anything, increases (280). In rabbit nerves the amount disappearing at first, 33 mgm. per cent per hour, would, if all burned, about account for the oxygen consumed. The rate of disappearance, however, falls rapidly with time and the sugar usage has practically stopped, as the supply is exhausted, in about 3 hours (367, 368). The rate of oxygen consumption, however, though slowly falling during this time, is still well over one-half of its original value. Obviously if the sugar is all being burned, the nerve is able smoothly to introduce more and more non-sugar as its fuel. (The possible use of cerebrosides, containing galactose, is not excluded, though there is negative evidence for brain, 562.) A similar use of non-carbohydrate fuel by muscle is now also recognized (578, 529, 531, 354).

Bullfrog nerve also exhibits a fall in sugar of 6 mgm. per cent per hour

during aerobic rest, but, like its respiration, the change here is linear with time for over nine hours (368). Oxygen consumption, R. Q. (after an initial excess), and sugar loss continue at a constant rate, but one cannot draw the obvious conclusion that a constant fraction of the resting energy is obtained by carbohydrate oxidation. If all the sugar disappearing were fully oxidized, it would require half again as much oxygen as actually consumed. More likely it is only partially oxidized and end products slowly accumulate (also in harmony with the low R. Q.). *In vivo*, if reactions lead to the same end, the products would be removed in the blood stream or their oxidation subsequently completed during activity. Further, all free sugar has disappeared from these nerves long before any change in respiration is manifest; so that, quite clearly, any sugar being burned at first is fully supplanted later with no hitch in the respiratory (or conducting) mechanism. In green frog nerve, Winterstein and Hirschberg (774) report a decrease of 280 mgm. per cent of "alcohol precipitable sugars" in 24 hours, the nerve content falling from 500 to 220 mgm. per cent. These values are so high that much non-carbohydrate material was probably included. The large amounts of sugar disappearing from solutions containing nerves, as found by these workers (358), are also difficult to understand. The rate of loss of glucose at rest at 15° averaged about 12 mgm. per cent per hour over 24 hours, slightly more for galactose; and other metabolic changes were found concurrently. Further, the absolute increased disappearance on stimulation was so great as to preclude its oxidation. The possibility exists that much of the sugar was simply taken up by the nerve or changed in other ways.

The relative unreactivness of nerve glycogen, especially during rest or activity in oxygen, raises suspicion as to its true chemical nature. Brain glycogen, however, appears to have been thoroughly identified (688, 369, 384, 691, 561, 644, 645, 364, 562) with the liver substance; yet it is also relatively inactive. True and pseudo glycogen have been distinguished in nerve cells (645, 646), the latter probably more inactive, and a small unreactive residue in muscle has also been reported (400).

b. *Ammonia.* This will be discussed, more conveniently, with the the metabolism of activity.

c. *Phosphorus.* During rest, the total acid soluble phosphorus of nerve increases at the expense of the insoluble fraction. The increase is distinctly greater in nitrogen than oxygen (280). Experiments are in progress to determine whether, as seems probable, this represents a breakdown of phospholipin. (This increase has not appeared regu-

larly in current experiments.) It might be noted here that the presence of an oxidizing reserve in nerve (see later) would permit some oxidations to continue even in a nitrogen atmosphere for a limited time. The total and acid soluble phosphorus of green frog nerve shows considerable seasonal variation. The acid soluble fraction increased from 34 mgm. per cent in the fall to 50 in the winter, with almost no overlap of values in over thirty experiments. Of the acid insoluble portion, 60 mgm. per cent was dissolved in acetone on repeated extraction, and 195 mgm. per cent of the remainder by absolute alcohol, leaving 40 mgm. per cent of non-lipoid phosphorus in the residue. (Winter pipiens nerves, 279.) The acid soluble fraction (34 mgm. per cent) includes 5+ mgm. per cent pyrophosphate phosphorus (= 8 mgm. per cent adenyl triphosphate) and 14 mgm. per cent of phosphate compounds hydrolysed hardly at all on boiling for two hours in N/10 HCl. Neither of these fractions is altered during rest in oxygen (279).

B. *Anoxic Behavior.* The resting nerve, as also most other cells studied (but not all; 523, 267), enters into a glycolytic habit when respiration is suspended. Such activity results when oxygen is excluded or its utilization prevented by respiratory poisons.

1. *Glycolysis.* The lactic acid formation by frog nerve was studied by Gerard and Meyerhof (275) using mainly the manometric method mentioned, dependent on carbon dioxide liberation by a stronger acid, but checked by direct analysis for this substance. At 15°C. the onset of acid production is gradual, but little being formed within two hours. Accumulation then rapidly increases to a maximal rate of 7 mgm. per cent per hour at 3 hours, and slowly falls again. The maximum formed, 100 mgm. per cent, is not reached in 24 hours. At 28°C. the initial lag is much reduced and the maximal rate increased three times, a Q_{10} of 2–3, but the total formed is unchanged. This total lactic acid is approximately equivalent to the total free sugar present, so that its formation is limited by exhaustion of precursor. That such is the case is further demonstrated by addition of glucose to the Ringer, for then lactic acid forms at a rate constant, after the initial lag, and 50 per cent faster than in the absence of glucose, for days or until the added sugar has been used up. Neither galactose nor fructose can substitute for glucose here.

The accumulation of lactate ion or the depletion of nerve alkali (to the extent that this is not compensated by the solution of bicarbonate) is without influence on glycolysis within wide limits. After a day in glucose, very large amounts of lactic acid have been formed (300 mgm.

per cent, not all in the nerve), but the rate is still maximal. Further, whether the nerves are kept in a minimal amount of Ringer or in ten to twenty times as much is without influence on glycolysis. Since the concentration within the nerve of any diffusible metabolites (as lactate is) is thus greatly varied without any resulting influence on glycolytic rate, it may be concluded that there is no "toxic" or depressing action of such metabolites on this process. (Compare with muscle, 528, and the very different situation in Sarcina, 267, 262.) This point will be returned to in connection with activity during oxygen lack.

In rabbit and bullfrog nerve (367, 368) a more complete chemical balance has been demonstrated. In oxygen, glycogen remains constant, as does the concentration of lactate present or added, while sugars gradually disappear. In the absence of oxygen, free sugar disappears about as before and also half this amount of glycogen, the combined loss being fully accounted for by the increase in lactic acid.

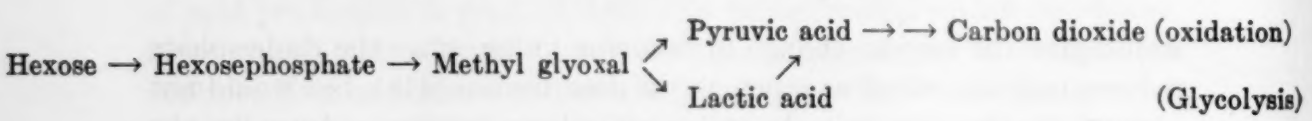
This balance seems almost too good, since it was found that the acid-stable phosphate fraction of nerve also decreased during anoxia (280) and, if it represents a hexose-monophosphate, should have supplied a considerable fraction of the lactic acid. Since the reducing value of a mole of hexose-phosphate is only two-thirds that of free sugar (178, 449), less reducing value should have been lost than lactic acid appeared. The reaction

$$2 \text{ hexose-monophosphate} \rightarrow 2 \text{ lactic acid} + \text{hexose-diphosphate}$$

would give the correct change in reducing value, since the diphosphate reduces only one-third as much as the free hexose (448), but would not account for the change in the stable phosphate fraction. Actually, the phosphate in the more specific hexose-phosphate fraction does not decrease during anoxia (367). Further, our most recent work (279) indicates that the acid-stable phosphate fraction in nerve is composed of at least one-third adenyl-pyrophosphate, which can completely break down during anoxia and so account for changes in this fraction; and that any small amount of hexose-monophosphate which may break down (beyond that reformed) is not sufficient to disturb the balance. The possibility must also be considered that the glycolytic mechanism of nerve resembles that of cancer (41, 324) and brain (29) and certain lactic acid bacteria (228) rather than that of muscle and yeast, and does not involve the step of phosphorylation of the glucose molecule. (It will be recalled, however, that phosphate ion does increase nerve respiration, 260, 656). Work in progress on the acid-stable phosphate fraction of nerve may clarify these points.

The oxidation quotient of nerve (that is, the extra lactic acid appearing when respiration is stopped, divided by the lactic acid that could be oxidized by the oxygen respired normally, both in mols per unit time and weight) is 3.0 in Ringer. Addition of glucose increases lactic acid production but not respiration and brings the quotient to 4.5, similar to values for muscle. Oxidation of one molecule of lactic acid or its equivalent is able, therefore, to prevent the formation of three or four molecules of this substance. It seems simpler to consider the influence of oxidation here as preventing the acid formation rather than as continually leading to its restoration to carbohydrate, for once lactic acid is formed in nerve (aside from a hypothetical "nascent state") it is not removed by oxidation or resynthesis. There is also good reason to believe that lactic acid formation in nerve can be prevented by oxidation of non-carbohydrate. Aside from the low R.Q., not raised by glucose, is the further direct evidence, already discussed, that some time after isolation, when oxygen consumption remains high and conductivity is retained, no sugar is being oxidized. Yet aerobic lactic acid formation does not set in. The interesting suggestion, made by Dickens and Simer (146, 147) in connection with their cancer studies, that lactic acid formation is prevented only by carbohydrate oxidation, would thus appear to be invalid, at least as a wide generalization. (See also 531, 354.)

A current scheme of sugar oxidation and glycolysis is:



Recent evidence, especially from iodoacetate studies (156, 421, 531) confirms the view that methyl glyoxal is a precursor of lactic acid. Glyoxalase activity, for example, is interfered with by this reagent (156, 470). It appears, further, that concentrations of the halide that prevent glycolysis also interfere with the oxidation of sugar (421, 531), and it is suggested consequently that lactic acid is on the main path of carbohydrate oxidation (421). This is, of course, only one possible interpretation, since interference with the further change of methyl glyoxal itself would directly affect sugar oxidation as well as its glycolysis. Also, the halide, in small concentration, acts directly upon the glycolase system (470). Methyl glyoxal has been demonstrated in muscle (110) and when added to muscle brei disappears as well from poisoned as untreated tissue (43), as does also lactic acid (531). Studies

on heart likewise (36) indicate that carbohydrate oxidation does not involve fermentative changes, and some yeasts easily burn maltose but are unable to ferment it (712). For nerve also it seems that lactic acid is an alternate rather than an intermediate of carbohydrate oxidation, since galactose is easily burned but not glycolysed, and since lactic acid once formed is not oxidized. Iodoacetate does not interfere with the oxidation of lactic acid by muscle but does block its resynthesis to glycogen (531), so that lactate oxidation, when it does occur, may be entirely independent of carbohydrate formation or oxidation. Apropos the mechanism of iodoacetic poisoning, it is significant that this substance blocks cancer glycolysis as well as that of muscle (261, 325), although in this tissue phosphorylation of carbohydrate is not an intermediate step.

It is in fact doubtful to what extent the Meyerhof cycle is of general validity, however well established for normal muscle. In most other cells where the disappearance of several molecules of lactic acid for each one oxidized has been demonstrated, it has been assumed that these were reformed into carbohydrate. In the case of brain, Takane (689) did not find such a resynthesis and Holmes and Ashford (366) were unable to demonstrate an increase in carbohydrate, although the typical oxidation quotient of 3–4, with the disappearance of considerably more lactic acid than could have been burned, was obtained. They have been unable to demonstrate accumulation of pyruvic acid or other partial oxidation products (30) and its fate remains unknown.

2. *Phosphocreatin.* When a nerve is deprived of oxygen, the phosphocreatin is broken down rapidly at first, then slowly. This has been demonstrated alike from a study of "labile-phosphate" and "bound creatin," the results on both agreeing well (280, 277). A similar situation is well known in skeletal muscle (171, 213, 214) and has recently been found in the heart (118) and in the electric organ of the torpedo (405). When glycolysis is suspended as well by treatment with monoiodoacetate, the breakdown is more rapid (278), but increasing glycolysis (261) and furthering certain oxidations with methylene blue (113) does not diminish the breakdown. The dye also increases liver glycolysis (635). In muscle, even more strikingly, though this dye increases anaerobic glycolysis ten times or more, it greatly enhances the breakdown of phosphocreatin (261, 278). These points will be more fully discussed below.

Carbon dioxide, even in 5 per cent concentration in the gas, also leads to a decomposition of phosphagen which, in pure carbon dioxide,

is maximal in fifteen minutes. This breakdown, as also that of anoxia, is easily reversible when normal conditions are restored.

3. *Acid-base balance.* It is desirable, in connection with the lactic acid and creatin phosphate changes, to consider the acid-base picture in nerve. The much smaller effect due to ammonia production and inferred breakdown of adenylic-pyrophosphate (to inosinic acid, ammonia and two molecules of orthophosphate) and to changes in esterification, can probably safely be neglected. Creatin phosphate is a stronger acid than the split orthophosphate (214, 533) so that its breakdown tends to diminish acidity. The actual changes are as follows.

At rest in oxygen there is no significant shift in any of the important constituents and the pH and buffers remain constant. During anoxia there is a breakdown of phosphagen and formation of lactic acid. In 2 hours there is formed, as determined by chemical analysis, about 15 mgm. per cent of lactic acid, or 1.6 micromoles per gram nerve. At 4 and 20 hours the values are 3.9 and 6.2 micromoles. Manometrically determined, the values at the same times averaged 1.1, 2.8 and 6.6 micromoles. It will be noted that at first the manometric values fall below those directly determined by 0.5 and 1.1 micromoles, while later there is no deficit. The phosphocreatin breakdown is largely complete in an hour, when slightly less than 2.5 micromoles have been hydrolysed. At 20 hours the value is 2.5. In many experiments, especially on lactic acid, the nerves were in chambers with 5 per cent carbon dioxide in the gas phase and 0.03 molar bicarbonate in the Ringer, from which values the pH may be calculated by the Henderson-Hasselbalch equation (328, 717) as 7.38.

$$pH = pK_1' + \log \frac{HCO_3^-}{CO_2} = 6.27 + \log \frac{0.03}{0.0023}$$

(See 461.) This is about the pH estimated for frog nerve *in vivo* by Fenn (203). At this pH, one equivalent of phosphagen liberates, according to Lipmann and Meyerhof (461), 0.21 equivalent of base; according to Fiske and Subbarow (214), 0.29. Taking the mean, 0.25, the phosphocreatin broken down during anoxia should liberate 0.6 micromole of base. This is obviously of the proper magnitude to cover the difference between lactic acid determined chemically and that determined by displacement of carbon dioxide by the stronger acid. Actually, the data are hardly sufficient to make this calculation more than indicative; but it is worth noting that by both methods of determining lactic acid, even after correcting the manometric one for phosphagen

loss, there is an initial lag in the onset of glycolysis after the establishment of anoxia.

In oxygen, there is no lactic acid production on stimulation; in nitrogen no excess over the resting change. Stimulation in either gas, however, leads to an increased loss of creatinphosphate. During two hours tetanus in oxygen, 5 mgm. per cent of creatin or 0.38 micromole of phosphagen breaks down, with the liberation of 0.1 micromole of base per gram or a change of 0.1 millimole in molarity. To pass from pH 6.4 to 7.2 requires 22 millimoles change (203), so that this would involve a pH alteration only in the third decimal.

Carbon dioxide likewise leads to loss of phosphagen. In 5 per cent carbon dioxide this amounts to 0.15 micromole per gram; in 100 per cent carbon dioxide, to 0.53. This represents a liberation of 0.04 micromole base by 5 per cent carbon dioxide, using an equivalence factor of 0.25. In 100 per cent carbon dioxide the pH is 6.15 and the factor 0.8, so that 0.42 micromole of base is freed. If the base were neutralized by extra carbon dioxide absorbed, one micromole of base would require 22 cmm. of carbon dioxide per gram, or 2.2 vol. per cent. In 5 per cent carbon dioxide, 0.1 vol. per cent; in 100 per cent carbon dioxide, 1 vol. per cent of the gas would be so absorbed. These are therefore only negligible corrections to Fenn's carbon dioxide absorption curve for nerve. In the case of muscle, very considerable corrections result—20 vol. per cent in 100 per cent carbon dioxide.

4. *Oxidizing reserve.* At the beginning to the present century, evidence for an oxygen reserve in muscle (in the form of an inogen molecule in then current theories, 337) appeared convincing. In nitrogen the tissues continued to liberate carbon dioxide, more during contraction—which function was preserved—and when oxygen was again made available an extra amount of this gas was consumed, presumably for storage. The work of Fletcher (216, 217) and Hopkins (218) substituted the lactic acid mechanism in physiological thought. Anaerobically this substance accumulates, faster during activity, and displaces a corresponding amount of carbon dioxide from fixed base. In the presence of oxygen, later, an extra amount of the gas is taken up, not for storage but due to the presence and for the oxidation of lactic acid (532). Carbon dioxide is not actually produced anaerobically nor is an oxygen depot exhausted (525, 526).

The evidence that an oxidizing reserve does exist in nerve appears at first similar to the inadequate evidence for muscle, but the important difference obtains that in the experiments on nerve the total carbon

dioxide in the tissue as well as that liberated has been determined. Simple driving out from preformed bicarbonate could thus not alter the total, and any increase should represent an actual formation. Speaking, then, in terms of carbon dioxide formed, a store of oxidizing substances in nerve should lead to a shift forward into the anoxic period of some of the carbon dioxide formation. Starting anoxia with an oxygen reserve, oxidations would continue till this was exhausted or much reduced, with an attendant carbon dioxide production. In readmitting oxygen gas, an excess of this should be taken up to replenish the store without an equivalent excess of carbon dioxide formation. (If during anoxia oxidations did not run to completion, less carbon dioxide would be formed then and would appear as a lesser burst when oxygen was restored.) An excessive oxygen consumption following anoxia might be destined, then, for 1, replenishment of the oxidizing reserve, and 2, carrying out extra oxidations needed to restore the resting state (of the nerve membranes?). The carbon dioxide formed anaerobically represents the end product of oxidations with the oxidizing reserve; any excess formed after asphyxia results from 1, the completion of extra oxidations as indicated in 2 above, or 2, the completion of oxidations carried only part way during the anoxic period. If the same reactions occurred in oxygen lack as normally, the R.Q. for the entire period of anoxia and recovery to previous rates should be the same as at rest in oxygen.

These criteria have been met. Gerard (253) demonstrated a continued formation of carbon dioxide at an average of 10 per cent of the aerobic rate during a 20-hour period of anoxia. This was confirmed by Schmitt (650), who also showed that for shorter periods the hourly production was greater. At 2 hours, for example, the anaerobic carbon dioxide is almost half the aerobic. Following anoxia, an excessive amount of oxygen is taken up (253, 204, 205), and a much smaller quantity of carbon dioxide produced (204, 205), or none at all (650). The R. Q. for the whole episode must be pieced together from separate data, not always comparable, but a fair calculation indicates values in the proper range (table 3). Another bit of evidence favoring the existence of such a reserve is the slow onset of glycolysis. Further, small fibres, with a large surface to volume ratio, fail faster than larger ones during anoxia (332, 257, but see 453) or narcosis (579). Also the rate of breakdown of phosphocreatin when gaseous oxygen is simply excluded (and the amount physically dissolved in nerve must diffuse out or be used up within 5 minutes, 255, 348) is slower than when oxidations

are blocked by respiratory poisons, such as cyanide or monoxide (278). Conduction fails more rapidly in cyanide than in nitrogen (195), though this was not found in nerves without the sheath slit (656), nor was there any difference between failure in monoxide and nitrogen (651).

The nature of the oxidizing reserve is conjectural. Many substances are now known to be actual or potential intermediates in the series of reactions of respiration. These are in balance between oxidized and reduced state and whatever fraction is oxidized at the time further oxygen supply is cut off may still be reduced in the normal fashion. Oxidized glutathione and cytochrome, as well as other $-S-S-$ and Fe^{+++} compounds, if present in sufficient amount relative to the respiratory

TABLE 3

HOURS ANOXIA	CO_2 FORMED DURING ANOXIA PLUS EXCESS AFTERWARDS	O_2 EXCESS TAKEN UP AFTER ANOXIA	R.Q.
	cmm. per gram per hour anoxia	*cmm. per gram per hour anoxia*	
2	7.1*	10†	0.7
4	5.5*	2.7*	0.5
	30‡	15‡	0.5
6	3.7*		
	20‡	7.3‡	0.4
15	1.6†		
	1.6*	1.4*	1.1

* Data from Schmitt (650).
† Data from Gerard (253).
‡ Data from Fenn (205).

rate, would obviously serve in this manner. An estimate (254), based on the glutathione content of brain (363, 373) assumed for nerve, indicated that this could supply oxidizing capacity equal to that required for resting and active metabolism for one hour. Methylene blue, since it is reduced by nerve, might play a similar rôle when added, and like considerations apply to metadinitrobenzene (462), but these must be discussed in another connection. A somewhat analogous situation exists in luminous bacteria (327). During oxygen lack the normal balance of oxidized and reduced luciferin is displaced towards the latter and, as a consequence, when oxygen is again admitted the light produced is for a moment much more intense than the maintained level, due to the larger amount of reduced luciferin reacting.

If such respiratory intermediates are indeed involved, a similar or greater oxidizing reserve might be anticipated in muscle with a more concentrated catalytic system. It may indeed be present, and should be looked for more carefully, but would have been missed in ordinary experiments with muscles activated in nitrogen. (Meyerhof, 525, however, reports two experiments showing none.) The energy liberated during muscle activity is thousands of times that in nerve, and any small oxygen reserve would be swamped by the great lactic acid changes. Finally, it may be noted that if respiratory poisons render non-available the reserve as well as free oxygen, then the reserve must be in a form blocked by them. Such would not be the case for cytochrome, for example. The evidence from phosphocreatin breakdown and the more rapid block by cyanide than simple oxygen lack would indicate such an action, but the monoxide results, and the fact that a nerve blocked in monoxide and restored in light continues to conduct for 30 minutes or more after the light is removed, and despite the prompt disappearance of oxygen consumption (651), suggest the reverse. The nature of the reserve, therefore, must be regarded as undecided. Other points concerning it will be discussed in connection with the active metabolism of nerve.

C. *Respiration Catalysts.* The little known concerning glycolytic mechanisms in nerve has been mentioned, and these are at best of secondary importance under normal conditions. In the body, the blood supply of nerve is fairly abundant (613, 711, 413, 614) and *in vitro* adequate oxygen penetration is easily obtained, so that it is doubtful if glycolysis is ordinarily called into play by the resting nerve; and a lactic acid mechanism appears to be excluded for activity under any conditions.

The respiratory catalytic systems seem to adhere to familiar types. Washed nerve brei contains dehydrogenases in the same sense and for the same class of substrates as does muscle (707, 708, 367). Glutathione is present in small amounts, though cytochrome has not been clearly demonstrated (367, 548). Oxidases of the indophenol group have been found (367). Respiration can be largely inhibited by cyanide (275, 656, 112, 113), but not completely even when its absorption by alkali is avoided (275, 656); or by carbon monoxide, this latter being reversed by light (652, 651, 113). N/50 cyanide does not disturb glycolysis (275). (It is claimed that N/1000 cyanide stops brain glycolysis, 507.) A breakdown of phosphocreatin, as in anoxia, results from the addition of cyanide, monoxide, or hydrogen sulphide (278),

and the possibility of active conduction is lost following progressive depression (195, 419, 654, 656).

A short digression into general theories of cell oxidation may facilitate further discussion. The older dichotomy of views resulted from emphasis on activation of oxygen or hydrogen. The usual substrate does not react with oxygen in a test tube but does so easily in the body; hence the gaseous oxygen or the substrate or both must be activated. Warburg (741, 743) emphasized the former, insisting on the important rôle of heavy metals (especially iron) in the catalysis; Wieland (763, 764), Thunberg (708), and the Cambridge school (371, 148, 321), the second. Warburg and his colleagues have brilliantly established the ubiquitous presence and activity of metal catalysts, especially the iron hemin compounds (739, 740, 742, 420, 748, 750, 751, 745), but whether these act in a unitary fashion remains an open question. Further, it is improbable that the "atmungsferment" simply activates oxygen, since analogous metal catalysts accelerate oxidations not involving this gas nor the transfer of oxygen atoms (e.g., oxidations by methylene blue, 762, 763, 320, 749). It seems that the conflict is being happily resolved in that the activators are metal complexes, as insisted by Warburg, but the activation primarily of substrate, as maintained by Wieland (see 746, 764, 747).

The use of cyanide to poison iron catalytic systems has been an important experimental method in the study of oxidation mechanisms. The long-maintained view, that all respiration is cyanide sensitive, and therefore dependent on iron, is not rigorously true (149, 35, but see 21). Even in tissues ordinarily inhibited by cyanide, such as nerve, there is often some residual respiration after its application (275, 149, 656). This residuum may be further decreased by simultaneous use of monoxide (115), or narcotics (208), or may spontaneously increase, possibly due to loss of cyanide from the cells (656). Another group of cells, especially unicellular organisms, is little if at all sensitive to cyanide. This has been recently demonstrated for sarcina lutea (262), colpidium (607), and paramecium (272, 671). A cyanide-stable respiration is not, however, necessarily independent of iron, since several ferrocatalysts, especially the hemin derivatives, are not at all interfered with or are even activated by this and similar agents (626, 301, 761, 730, 744, 787). On the other hand, it has been claimed (671) that paramecium is iron-free, which would, of course, be in line with a cyanide insensitivity. It appears as though final conclusions as to the participation of iron or other metal compounds in catalytic systems must not be based solely on the action of cyanide or similar poisons.

The exact position of cytochrome, and still more of glutathione, in the reaction chain is also contested and uncertain. Keilin (394, 395, 396) has attempted to prove, for the former, an intermediate location between active oxygen (activated by the indophenol oxidase—the respiration enzyme) which serves to oxidize cytochrome, and active substrate (hydrogen activated by the specific dehydrogenases) which in turn reduces it. This work has not passed unchallenged (321, 670), but oxidation of activated sugar by molecular oxygen does require the presence of the pigment as well as oxidase (322). Pure glutathione (372, 570, 399) does not possess the properties originally attributed to it (714, 518), but it does undergo oxidation and reduction in tissues (373), and its hydrolysis product, cysteine, in combination with metals appears very reactive as an oxidative catalyst (107, 518, 172, 174, 398, 675, 658; but see 282, 283, 727, 175).

Methylene blue had long been used as a substitute for oxygen in studying oxidations, but quantitative experiments were practically limited to special chemical systems or tissue brei. It is only recently that Barron and Harrop (326) discovered a marked increase of oxygen consumption (and decreased lactic acid production, 47), by mammalian erythrocytes when methylene blue was added. (An older observation, 401, of a similar action on killed staphylococci may be recalled.) Further work demonstrated analogous, but smaller, increases with certain other tissues, especially those possessing an aerobic glycolysis (45). The dye effect, however, is not limited to such tissues, as it is marked in nerve, muscle and others (260, 261, 262, 112, 113). Wendel (759, 760) and Warburg, Kubowitz and Christian (749, 751, also 755) soon showed that the dye oxidizes Fe^{++} hemin to Fe^{+++} hemin (in the blood cell, hemoglobin to methemoglobin), being itself reduced to the leucobase. Gaseous oxygen restores the dye on the one hand, and on the other Fe^{+++} hemin is again reduced with an attendant oxidation of substrate—such as lactic to pyruvic acid. This last step requires a two-component system to activate the substrate (746), and with it, methylene blue is able to oxidize the active substrate directly (747, 322, 46). Cyanide accelerates rather than inhibits the whole reaction (761).

The interactions between dyes and respiratory poisons and upon tissue oxygen consumption are especially interesting. Washed muscle brei plus succinate consumes oxygen freely and about equally in the presence or absence of methylene blue, or reduces the dye in absence of oxygen. Respiration, in absence of the dye, is largely abolished by cyanide, to be exactly restored by addition of methylene blue; and if this

substance is present from the start no inhibition results from cyanide. Rat sarcoma respiration, though behaving like muscle in most respects,—increased greatly by adding succinate to the washed brei, largely inhibited by cyanide,—cannot be restored by methylene blue after inhibition by cyanide (Fleisch, 215). This shows that the dye effect on muscle does not depend on any direct inactivation of cyanide by the dye, since this should be equally present with both tissues. (They do form an addition compound, but excess cyanide can be present, e.g., M/100 sodium cyanide and M/1000 methylene blue, with no change in results; also our controls show no significant oxidation of cyanide in the presence of the dye and oxygen.) The dye must act, therefore, either by releasing some elements of the respiratory mechanism blocked by cyanide, or by acting as a direct substitute for the blocked element.

We have fully confirmed Fleisch and extended the observations to intact muscle and nerve, and to combinations of methylene blue and carbon monoxide (113, 115). Whole muscle, without added succinate, acts much like the brei, though here the dye itself evokes a marked increase in respiration, and the return after cyanide inhibition is to a value between that of muscle alone and muscle plus dye but without cyanide. The oxygen consumption of nerve, as mentioned, is increased by dyes—up to 20 per cent by dichlor-orthophenol-indophenol, 70 per cent by methylene blue, and over 100 per cent by cresyl blue—and inhibited by cyanide. (The activity here is not in order of the oxidizing potential of the dye But see 542, 48, 543.) Respiration of an unstained nerve inhibited by cyanide can be restored to nearly its original value by methylene blue or cresyl blue (to 50 per cent higher values in invertebrate nerve, 112), though in both cases oxygen consumption falls with time, as also occurs with the dye alone. Using carbon monoxide in place of cyanide, intact muscle or the brei responds in the same manner to a dye addition, but intact nerve does not. The respiratory inhibition of nerve produced by monoxide is only slightly affected by cresyl blue (113). Hall (313) has been able to demonstrate the same relationship of cyanide and dyes acting upon the respiration of fish erythrocytes; and the respiration of B. coli responds to cyanide, monoxide and dyes very much as does that of nerve (125, 126).

It seems to follow that the actions of cyanide and carbon monoxide on the respiratory mechanisms of nerve are not identical. If the dye substitutes the affected link in the reaction chain, either different links are acted upon by the two inhibitors or carbon monoxide acts upon the

same one as cyanide and another as well. (It has been shown that methylene white is mainly not autoxidizable but requires a metal or surface catalysis for its reoxidation, 620. Further work, 125, shows that the catalytic metal, probably copper, is blocked by carbon monoxide but not by cyanide. This would seem to account for the above results, except for the fact that often large amounts of dye were used—up to 0.2 per cent—and much remained in the oxidized state, so that reoxidation of the leucobase was not essential in the system.) If the dye frees the normal mechanism from block, which seems less likely, then it must be that the monoxide-catalyst combination in nerve is less easily reactivated by it than is the cyanide-catalyst one, whereas they are alike activable in muscle. Experiments with yeast have roughly paralleled those with nerve. Cresyl blue (but not methylene blue, which does not penetrate) increases oxygen consumption of these cells and somewhat counteracts cyanide inhibition. It is interesting to note that many agents—chloroform, monoxide, water, aluminium chloride, acid, etc.—cut out a little over two-thirds of the respiration of nerve. The residual portion may be different from the more sensitive one in catalytic systems or substrate. The oxidation of unsaturated lipins, for example, may be related to glutathione and is relatively insensitive to inhibiting conditions.

Studies of nerve creatin (277, 278, 264, 279) partly supplement those of respiration. This substance is present in nerve in three fractions—free creatin and phosphocreatin extractable with trichloracetic acid, and a small residual amount, presumably combined with a larger molecule, such as protein. Hydrogen sulphide breaks down $\frac{2}{3}$ of the creatin phosphate in 10 minutes, irreversibly. Cyanide causes a similar, but reversible, breakdown and carbon monoxide also, reversible in the latter case by light as well as oxygen. After such a decomposition and reformation, a small consistent increase of the residual fraction is regularly observed. Methylene blue has no effect on the creatin distribution in nerve, nor does it decrease the loss of phosphagen resulting from asphyxia or the respiratory poisons, except for a slight protective action against cyanide. The apparent conflict between the capacity of the dye to restore oxygen consumption after cyanide and its inability to restore phosphocreatin (or conduction) is probably dependent on energy relations, to be discussed. Interference with oxidations affects the creatin phosphate of muscle as that of nerve, but methylene blue acts very differently. Added to muscle, even in oxygen, the dye leads to a marked loss of phosphagen, and when combined with asphyxia,

cyanide or mincing, the breakdown due to these factors is increased. It is difficult to understand why this dye, while increasing respiration and glycolysis, should enhance the breakdown of phosphocreatin. Some "toxic" effect on enzyme activity (612), not further defined, may be involved; or a possible explanation be sought again in terms of the energy exchange of the system.

D. *Energy Relations.* 1. *Sources.* It is well known that the energy required by animal cells is released almost exclusively from chemical stores by election transfers. These oxido-reductions involve either separate molecules, as foodstuff and molecular oxygen, or parts of the same molecule, as in fermentations. It is common practice to speak of the substrate as yielding energy on oxidation, as glucose gives 673,000 calories per mole on oxidation, with a consequent neglect of the oxidizing elements. This is almost surely incorrect. An atom is oxidized as electrons are pulled from it, and separating the negative charge from a positive kernel does not yield but requires energy. Energy is freed, however, when the electron falls into another atom being reduced; and the energy balance of any reaction is, then, that liberated by the reduction less that required for the oxidation. Combustion heats have been successfully calculated on this basis (Kharasch, 401). When glucose is oxidized by oxygen, which yields large energy on reduction, the above figure holds, but not for oxidation by other substances. The easily reversible systems, such as methylene blue-methylene white, are changed with far less energy shift than $O_2 \rightarrow 2O^{=}$; so that reactions of substrate with oxygen that are strongly exothermic might be even endothermic with methylene blue. For a particular case of the oxidation of methyl alcohol to formaldehyde, Meyerhof (524) has shown that when oxygen is the hydrogen acceptor the heat is twenty times greater than when methylene blue serves this rôle.

In biological systems, consequently, though certain oxidations may be effected by either oxygen or methylene blue,—even to the complete breakdown of substrate to carbon dioxide, water, etc. in both cases—the energy so made available must be widely different. By comparing the behavior of cells using oxygen or methylene blue as oxidizer (or hydrogen acceptor) much crucial information may be obtained as to the significance of metabolic events. Any one oxidative reaction in a cell may be valuable as a means of 1, obtaining energy; 2, removing an undesirable material (especially with oxygen as acceptor), or 3, synthesizing a desirable substance. It seems very likely that the ordinary food substrates are oxidized by oxygen when the cell requires energy,

but by organic intermediates which undergo reductive synthesis during times of growth or repair. A specific case will illustrate the point. Washed muscle brei plus succinate as hydrogen donator reduces oxygen, as this accepts hydrogen, to peroxide and water. This same system also reduces phenyl pyruvic acid, as hydrogen acceptor. In the presence of ammonia, phenyl alanine is formed (preliminary results, unpublished). The first reaction leads to a considerable freeing of energy; the second to specific synthesis. (It will be recalled that Embden, 182, 183, obtained phenyl alanine and alanine by perfusing liver with the ammonium pyruvate salt, and Knoop, 183, 134, 410, was able to obain a phenyl amino acid in vitro only by reducing the α ketonic acid in the presence of ammonia, never from the α hydroxy acid by direct aminization. See also 57.) A formation of fat from sugar involves analogous reductive syntheses. To the extent that any oxidation is important to a cell for its energy yield, methylene blue cannot replace oxygen as oxidizer. Where some accumulated material is to be removed or other formed by oxidation, methylene blue, if it oxidizes at all, will be as effective as oxygen. The reductive syntheses (or removals) are in a separate category.

These considerations help explain many of the effects of methylene blue on nerve and muscle. For further discussion see Gerard (265a).

2. *Utilization mechanism.* The yield from the primary energy liberating reactions is physiologically useful only in so far as it is free energy; and even this, unless directed through some physico-chemical mechanism, is lost as heat. It is important that the free energy may considerably exceed the thermal energy in glycolyses but is about the same, up to 6 per cent greater, in oxidations, (102). A major problem of cell physiology is the elucidation of these mechanisms. In muscle, a chemical sequence has been uncovered involving several members. The known chemical change most directly associated with the contraction, and its most immediate known energy source, is the breakdown of phosphocreatin. This exothermic reaction is reversed and the phosphagen restored by energy from oxidations or glycolysis, the latter being itself ultimately reversed by oxidative energy (479, 480, 536, 481, 210, 350, 351, 535, 336, 531, 111). There is considerable evidence that adenyl triphosphate may break down to give the immediate energy for phosphagen resynthesis, being in turn rebuilt by energy from oxidation or glycolysis (534, 178, 354, 44). Evidence has been presented above for an analogous system in resting nerve. When oxidations are prevented by removing oxygen or poisoning the respiratory catalysts,

lactic acid production increases and phosphocreatin breaks down. If, in absence of oxidation, glycolysis is also interfered with by sodium iodoacetate, the functional capacity of nerve is lost sooner (Ronzoni, 629) and more phosphocreatin breaks down (278, 354), whereas in the presence of adequate oxidative energy, blocking glycolysis does not have such effects. (See also 119 on heart.) Though the coupling mechanism is unknown, it is clear from this that it is not the chemical changes associated with oxidations but the free energy so made available that is important in preventing glycolysis or phosphagenolysis. (It is significant that iodoacetate appears to interfere with the coupling of oxidative energy with the recovery mechanism in muscle, 210, 111. But see 331, 785.) Methylene blue, even if substituting oxygen without altering the oxidation reactions, would not yield the energy to prevent these breakdowns. With methylene blue and oxygen both present, the dye will have an influence only if it serves as hydrogen acceptor easily relative to oxygen. Thus a possible explanation of the phosphagen breakdown induced in muscle by the dye alone is that oxidations occur preferentially with the dye rather than oxygen as hydrogen acceptor. The energy liberated within reach of the cell mechanism is therefore much reduced and the large energy amount, when oxygen is reduced by the methylene white, is freed in structureless solution and so entirely lost. The failure of the dye to cause a similar phosphagenolysis in nerve may depend on its much poorer diffusion relative to oxygen in nerve as compared to muscle, or to differences in the oxidative systems. Certainly the increased respiration and glycolysis evoked by methylene blue in muscle are much greater than in nerve (260, 261). The dye may, of course, have other effects, especially catalytic ones, independent of the energy relations. The interesting observation (51) that very small amounts of methylene blue greatly increase the anaerobic activity of muscle may be recalled in this connection.

3. *Uses in relation to structure.* Practically all living cells respire continually, using oxygen and freeing energy. If oxidation of foodstuffs is prevented, larger amounts of them are fermented—presumably because a needed energy quantum must be obtained and less is available per mole fermented than oxidized (see, e.g., 683). This energy flow continues in the absence of all external manifestations of activity or work, when cells are not contracting, conducting, secreting, luminescing or even dividing. Yet this energy is somehow essential, for cells deprived of it finally die. Warburg (733) early suggested that this resting, "basal," cellular metabolism was needed to maintain

the cell machinery, especially the surface structures (53, p. 593). Life is a dynamic equilibrium, not a static one, and cell differentiations, structural and chemical, are maintained despite homogenizing influences only by a continuous energy expenditure. The maintained integrity of membranes and of their electrical and osmotic properties is an important case in point. In the course of anoxia these should then lose their semipermeability and with it any polarization and potential and osmotic differences existing across them, and permit mixing of and reaction between substances normally kept separate. It is interesting that some bacteria which have apparently no "resting" metabolism are also unaffected by great osmotic pressure changes and behave like little more than packets of enzymes (including autocatalytic ones). Hill (350) has recently marshalled data bearing on these points for muscle, (this has been questioned, 303, 564), and various marine organisms, and similar relations hold for luminous structures. Thus Harvey (327) has shown that on oxygen deprivation Noctiluca enters into a period of steady luminescence prior to extinction. Lund has made a similar analysis of the behavior of seedlings (477), Obelia and other organisms or tissues (478), relating potential to oxidation processes. (See also 98 for an interpretation of analogous relations.)

The resting or injury potential of nerve is known to depend on the intact regions of the fibres, the injured end serving only as an imperfect lead from the inner core. (*E.g.* potential depends on the temperature of the living, not of the injured region, 60, though not linear with it, 416. This is not rigorously true, 232, 723, 597; nor should it be, since the injured end is promptly repaired to some extent and so does contribute to the potential, 75, 257.) A membrane of the axone is therefore normally polarized, maintaining across it a steady P.D. of tens of millivolts. In the absence of a complete impermeability to ions, this can only be kept up by a continuous energy supply, and it should follow that when deprived of this the resting potential of nerve would steadily fall. This has been clearly demonstrated for oxygen lack on rabbit (413, 414), spider crab (231) and frog (257) nerve. It might be predicted that a combined block of respiration and glycolysis (anoxia and iodoacetic acid) would lead to a still more rapid fall in the potential. Similarly, since the polarization is positive outside, negative within, it should require more energy than normally to maintain the membrane in the cathodal region of a constant polarizing current, less in the anodal region. The oxygen consumption of nerve should thus increase at the cathodal, decrease at the anodal regions when a constant (non-blocking) current is passed through it. This experiment also awaits performance.

Present views of the conducted nerve impulse involve a propagated membrane change with associated electric and chemical events (457, 458, 138, 95). An activated region becomes depolarized, permeable to ions, and so sets up local currents which excite adjacent regions. The ability to conduct will then depend very intimately upon the membrane condition. When this is completely or even partly depolarized, whether momentarily following a previous impulse or continuously as a result of slow changes in the resting state, conduction is impossible. During anoxia, frog nerve blocks when the resting potential has fallen only a fraction of its total (257) and a similar situation obtains for numerous other conditions (74).

On the other hand, of course, block may be induced by many other changes in the membrane. For example, an increased stability of the membrane, even associated with higher potentials, might prevent the action currents from producing a threshold change and so block conduction. This may underlie the action of another group of substances studied by Bishop (74 see also 300) which blocks action potentials while not affecting or even increasing the resting potential. The large volume of work, especially from Russian laboratories (359, 779, 781, 565, 491, 603, 718, 37, 756, also 628), demonstrating membrane changes and associated loss or return of conductivity of nerve under the influence of salts and polarizing currents, is beyond the scope of this review. The results consistently support the view that potassium ion blocks by rendering the membrane more permeable and so destroying its integrity, calcium ion by stabilizing it and making it too resistant to change. Cathodal polarization and alkalinity act as potassium, anodal polarization and acidity as calcium; and a block produced by one salt can be removed by the antagonistic ion or by appropriate polarization. The closely related problems of excitation must also be omitted here (433, 131, 227, 637, 636, 78). The relation of resting energy liberation and membrane condition to conduction will be discussed further in relation to activity.

It is to be anticipated that, following a period of anoxia, when oxygen is again admitted the cell structures will be rapidly repaired with the aid of oxidation energy. The extra oxygen taken up then would not only serve to pay off the oxygen debt and restore the oxidizing reserves, but also to further the needed excessive oxidations. The extra carbon dioxide produced following asphyxia is much less than the extra oxygen consumed (204, 205), which is evidence that the oxygen is indeed used in both ways.

A more intimate discussion of the nature of the resting potential of

nerve cannot be entered into. (See 360, 130, 361.) Concentration potentials of salts in two aqueous phases separated by a non-aqueous one (487), or a semipermeable membrane (60), or of electrolytes unequally distributed between watery and lipoid (68) or protein (510, 549) layers have been urged. Donnan potentials are not of sufficient magnitude, but may contribute, and are in the right direction (566, 550, 25). Redox potentials probably play a rôle and might easily serve as a direct link between the basic, oxidative reactions and the electrical manifestations (458, 477, 541).

Finally, it is worth noting that there exists normally a large factor of safety in conduction. The potential change accompanying activity of one region is much more than sufficient to excite an adjacent resting one. It is only when the action potential has been considerably lowered, the threshold raised, or both, that the impulse cannot propagate and block ensues (257). A quantitative study of these two elements under various conditions depressing conduction must yield valuable information. Such experiments with cold block are in progress, and data on respiration are in point. Resting oxygen consumption is probably reduced to a fifth or less of that at room temperature before cold block results. During anoxia, similarly, oxidations average less than one-third of the normal value during the two or three hours that conduction persists, and complete block does not ensue until the anaerobic carbon dioxide production has fallen to one-sixth the normal rate (204). It is interesting, as a comparison, that the development of fertilized sea urchin eggs is still normal at oxygen tensions of 11 mm., when their respiration rate has been cut to one-third, and can take place at 4 mm. when respiration is reduced four-fifths (22). (More recent work, however, has demonstrated a slowing of cleavage at considerably higher tensions, 692.)

E. *The Cell Body and Degeneration.* A nerve fibre separated from its cell body, like any cell region deprived of a nucleus, gradually dies. Since, in this case, the influence of the cell body must be exerted over relatively great distances, even meters, some definite mechanism must be involved. Such a "trophic" influence has been attributed to the neurofibrils (591) or axioplasm (64). Slow potential changes in nerve have been taken as a direct manifestation of it (725, 726), and prompt changes in irritability of a nerve after section from the cord (437) have likewise been considered as a result of its sudden removal. Recent analysis of various forms of "tonic" action of nerves has, however, regularly succeeded in resolving them into impulses of the well-known

discontinuous variety (229, 14, 79, 39). The reported threshold change has not been confirmed by one worker (408) and even if present, appears, according to still another (6), to depend on reflexes from the optic tracts or thalamus (438) rather than on the motor cell body itself.

Excluding, then, a somewhat mysterious and ill-defined effect, pending its more rigorous formulation, there appear to be two types of influence possible. The cell body may control the peripheral fibre by sending chemical substances or physical changes along it. In the latter case, the usual nerve impulse might obviously serve to maintain a necessary local balance of metabolic activity at each region of the fibre. Longitudinal polarization and continued currents might play some directive rôle, as they seem to do in growth or regeneration of nerve fibres (26, 380, 117, 27), but here again almost surely by influencing the movement of substances.

There is much evidence for the spread of chemicals quite specifically along axis cylinders, and at rates seemingly far beyond those that could be attained by simple diffusion. Adrenalin (455, 417), tetanus and diphtheria toxins (522, 289) and herpes (289), rabies (290) and polio viruses (192) may be mentioned, the latter traversing the length of a monkey's cord in two days. In this case, the virus accurately followed the pyramidal tract from the motor cortex down the cord, even crossing at the decussation. Beutner (68) and Brinkman and Szent-Györgyi (90) have demonstrated the rapid spread (a meter in four seconds) of fatty acids, soaps, etc. along an aqueous-lipoid interface; and such a system is roughly present in nerve.

That nerve integrity does depend in part on a continued supply to it of specific substances is evidenced by degenerations in avitaminoses. Besides the well-known beri-beri from lack of B_1, a typical degeneration has been found in animals lacking A (378, 158). In both cases, a secondary effect on the nerve from general disturbances seems to be excluded by starvation controls and the like, and restoration of the lacking accessory is the necessary and sufficient condition for prompt recovery. It has been claimed (386) that local application of vitamin B preparations could restore normal conduction in depressed nerve; alkaline Ringer, however, by counteracting an excessive tissue acidity, did likewise. Oxygen consumption of brain tissue from beri-beri pigeons has been increased in vitro by adding active vitamin (247; but see 306).

In the simpler case of a severed nerve, experiment definitely favors the view that interference with chemical transport is at the basis of

degeneration (123). Dog sciatics, left at rest or stimulated in situ following section, showed a more rapid loss of function with activity than at rest. Passage of impulses, therefore, accelerates rather than retards degeneration, just as activity accelerates metabolism. Similarly, action potentials in isolated frog nerves fail sooner in one tetanized and resting for alternate hours than in a companion resting except for brief tests (5). Conversely, pressure block of human nerves, maintained for months, can completely suspend function without any accompanying degeneration, since conduction reappears within an hour or two after the block is removed. In these cases, in contrast to the isolated stimulated nerve, conduction is stopped but structural continuity is retained, so that the travel of substances is not prevented. Other observations on the mantle nerves of octopus, which lose their function a few minutes after removal of the cell bodies in the stellate ganglion, have been given a similar interpretation (225); see also Scott's interesting results on frog dorsal roots (659).

Since nerve integrity depends on the availability of energy, ordinarily obtained by oxidations, an interference with the oxidative systems might be involved in the various forms of degeneration. Oxygen and substrate easily reach the axone via its own blood supply, but the catalytic substances necesssary to their reaction are not so readily available. If the respiratory ferment or accessories are formed only in the cell body (from the nucleus?) and continually travel down the axone where they are slowly destroyed in the course of the oxidizing reactions, much of the behavior of a severed nerve becomes clear. The cut fibres will lose their functional capacity and show cytologic change sooner the more rapidly the supply of respiratory agents, initially present, is diminished. This should occur more rapidly when the respiration is accelerated by repeated activity, as it does. Thyroid feeding also hastens loss of function of the cut nerve (124, but see 492) and increases its respiration (273). In cold-blooded animals the influence of temperature can be studied, and Rindone (625) found a Q_{10} of 2.2 for the degeneration of the frog's sciatic, a value in exact agreement with the Q_{10} of its oxygen consumption (253).

Further, there is evidence that in beri-beri and diphtheria also the nerve degeneration is directly related to a disturbed respiratory mechanism. There is less rapid oxidation of the Nadi reagent by the brain tissue of beri-beri pigeons than by normals (298), and similarly there is a prolonged reduction time of metadinitrobenzene (342, 343). Beriberi symptoms are closely duplicated by cyanide (342, 343). These

older results have, however, been seriously criticized (152). Corresponding to such depressed oxidations, there is *in vivo* a higher acidity (298) and lactic acid content (403, 404). To what extent acidity results from depressed respiration or, as the primary change, diminishes the latter secondarily is not clear. The possibility of a vicious cycle is obvious. Most recent evidence (1, 246, 247, 212) seems to favor a primary oxidative disturbance. It is interesting that mice on a galactose diet should develop beri-beri symptoms (307), since the brain cannot oxidize this sugar easily (468). Somewhat contrary evidence, however, indicates a disturbance of glyoxalase (728), which changes methyl glyoxal into lactic acid, and the immediate cerebral symptoms of beri-beri have been attributed to methyl glyoxal poisoning. Disturbances in the resynthesis of lactic acid to glycogen have also been invoked (306). It is not impossible to reconcile with one another all these factors (212).

The diphtheria toxin, which is able to travel along axones, is a heavy molecule containing much copper and some iron as an integral part of it (466). It has been urged, in fact, that the toxin represents part of the actual respiratory system of the bacilli, which can diffuse out of them and into body cells. Certainly these toxins are affected by cyanide, heavy metals, cysteine, etc., very much as the usual oxidation systems are (467; and see 301, 730).

The changes exhibited by a degenerating fibre are of autolytic character and not dependent on its remaining in situ. Isolated nerves, kept sterile in Ringer or serum or transplanted to another animal, show typical Wallerian degeneration (194, 379). Chemical studies on nerves left in position after section show a temporary increase in hydration and a marked loss of phospholipin (554, 315, 516), with liberation of choline (554, 315), phosphate and glycerine (501). In white matter of the cord, changes involve in sequence cholesterol, fatty acids and fat (686). Free amino acids are increased (501). There is also a marked increase in oxygen uptake (for the frog spinal cord, the maximum, at 3–5 days after section of the major tracts, is three times normal, 648), which seems directly related to an increased unsaturation of the fatty acids (672). The Marchi stain for degenerating fibres also depends on unsaturated lipin material, which reduces the osmic acid, and it has been used as a microchemical test for this (128). It is also reported (4) that after section of one sciatic in the dog or rabbit, the irritability of the other increases to a maximum value in 2 to 4 weeks and then returns to normal. This change is traced back to the liberation of stimulating

substances from the degenerating nerve into the blood stream. Irritability falls progressively (123) as does the injury potential (412), and block occurs in two to three days with loss of the requisite membrane state. Visible cytological changes are very slight at this time, but rapidly become more striking (101).

Besides the peripheral degeneration, an injured neurone shows a small amount of retrograde degeneration and chromatolysis in the cell body (569, 101, 681). These changes are but temporary and might be attributed to local injury currents, continued discharge of antidromic volleys from the point of injury (12), and the like. The cell alterations are much less marked when the axone is destroyed at a distance from the cell than when close to it (106). Later, regenerative changes ensue, and the axis cylinder grows out at a rate dependent on the metabolic level (youth, 544, thyroid feeding, 493, and high temperature, 625, enhance it). That the neurilemmal cells play some rôle in the regenerative process seems probable from their marked morphologic changes; but it is improbable, despite the current impression, that they are essential to it. Fibre growth in tissue culture (323, 103) and regenerative growth in the central nervous system (370, 145, 270) occur in the absence of any Schwann cells, as does normal growth in the tadpole's tail (680).

It would carry the subject beyond present limits to discuss the degenerative diseases of nerve and the central nervous system as appearing in man. An interesting point is that many of these are hereditary and almost certainly associated with gene deficits (52). Since these hereditary units are increasingly regarded as molecules of necessary enzymes, this group of disturbances may well fall into the same category as the ones discussed. A deficiency of oxidase in the brain cells in such diseases has been reported (503).

III. Active metabolism. In muscle, the evidence indicates that during activity the metabolic events of rest are greatly accelerated but otherwise essentially unchanged. This is not the case for nerve. In many qualitative respects the changes during activity differ from those of rest, and the possibility must always be kept in mind that some of the latter depend on non-nervous elements. Sugar, particularly, plays a large rôle in resting metabolism, both in oxidations and glycolysis, while seemingly concerned little if at all with activity. Since, however, the ability of nerve to respond to excitation depends so intimately on its resting metabolism, it is often difficult to discriminate, in any experimental situation, such as depressed oxidations, between influences on one and on the other.

A. *In Oxygen.* 1. *Heat production.* Many earlier attempts to measure the active heat production of nerve yielded false positive results due to unrecognized errors or false negative ones due to inadequate sensitivity (sometimes not realized) of the available apparatus. Elaborations of the technique developed by A. V. Hill in his myothermic studies (347, 593) permitted a quantitative study of nerve heat (151). Frog nerve tetanized for a few seconds gave an outburst of heat during and after activity. The total heat produced is obtained from the area of the galvanometer deflection-time curve, the initial burst of heat from the maximum deflection reached. Using 280 shocks per second at 15°C., the total heat produced per gram of nerve and second of stimulation is 6.9×10^{-5} calories, the initial burst about one-tenth of this.

Further analysis of the heat-production curve by means of a control heat curve, produced by passing currents through the nerve, showed that the nerve heat production falls into two distinct phases (254). The first, initial phase, accompanies conduction itself and does not outlast tetanization. There is, presumably, a brief intense outburst accompanying the conduction of each impulse and which, for short periods,is independent of other impulses; the initial heats for successive impulses are thus equal and simply succeed each other in time. The second, delayed phase, follows the actual conduction and continues with a gradual decline for ten minutes or more. The delayed heats of a series of impulses sum in magnitude (rate) but not in time, conversely to the initial phase. The maximal rate of initial heat production has been estimated to be some 5000 times the maximal of delayed, but the quantity of heat of the initial phase, due to its extreme brevity, is only 10.5 per cent of the total. Bronk (96) has repeated these determinations with improved apparatus and more accurate analyses and finds the initial phase constitutes 9 per cent of the total. His experiments were performed at a somewhat higher temperature than the earlier ones, and it will be important to determine any influence of temperature upon the ratio of initial to total heat (as well as their absolute magnitudes and durations). To the extent that the short range covered by Bronk's series and my own results permits an estimate, the ratio at a lower temperature is more than at a higher one. Thus at 15° the initial heat is 10.5 per cent of the total; at 19°, 9.5 per cent; and at 24°, 8.8 per cent or less.

(A. V. Hill has recently informed me of some preliminary results of a study of nerve heat production at low temperatures. At 20° he finds, per gram of nerve and second of maximal activity, an initial heat of

7×10^{-6} cal.; at 0° of 2.5×10^{-6}. Since, however, maximal activity at 20° is attained with 400 impulses a second and at 0° with only 30, the heat per impulse is several times more at the low than the higher temperature. This is related, perhaps, to the longer duration of changes in the cooled nerve.)

The total heat produced per impulse is very variable with the conditions of stimulation. Ten-second tetani with 280 shocks per second lead to equal heat productions when repeated at ten-minute intervals; to considerably less heat blocks when repeated at shorter ones, such as two minutes. When a change is made from longer to shorter intervals, each successive heat block is less than its predecessor, but by progressively smaller amounts until a new equilibrium level is reached and held (equilibration). Further decrease of interval causes a further fall to a new level; increase, a similar rise (255).

Change in shock frequency also changes the heat per impulse, this being maximal with the greatest interval between impulses. As the number of shocks per second increases, the heat per second does likewise along a roughly exponential curve. Two hundred and eighty shocks per second give a nearly maximal heat production per second, but each impulse gives little over one-fourth as much as does a single shock (271). The total heat per impulse traversing one gram of nerve fibre is, then, 10^{-6} calories; and the initial heat 10^{-7} calories. Using a fibre count of 3500 for a frog sciatic (159), this becomes 10^{-12} cal. total heat for a single impulse passing over one centimeter length of a single fibre.

For oleic acid, as an example, one molecule of which occupies a surface of about 21×10^{-16} sq. cm. (8), a mole would form a monomolecular film of 1.3×10^{9} sq. cm. The actual surface of the axiolemma of a centimeter length of axis cylinder of 8μ diameter is 2.5×10^{-3} sq. cm. and would require 3.0×10^{-13} moles to cover it. The total heat of a single impulse would correspond, then, to hardly 3.5 cal. per mole of acid on the surface; the initial heat to one-tenth of this value. The molar heat of complete oxidation is 2.6×10^{6} cal., and even for removal of one electron pair is about 50×10^{3} cal. (401). Such a partial oxidation could affect, therefore, at most one molecule in 14,000. If a single neurofibril of about 0.1 μ diameter, instead of the axiolemma of 8μ, were the conducting element, one molecule in 250 on its surface could react. This heat represents the total balance of the reaction and, conceivably, considerably greater energy changes might occur during one phase of the actual conduction, to be largely reversed during another.

2. *Respiration.* a. *Magnitude.* The increased respiration of nerve

during activity over that of rest has been studied by many workers using a variety of methods, based either on oxygen consumption or carbon dioxide production measurements. Although very wide variations in results have been reported, the more recent ones are in fairly good agreement, both for dogfish nerve (587, 199, 589) and for frog. The volumetric studies of Fenn (201) and the manometric ones of Gerard (260) on the sciatic nerve of R. pipiens are in almost exact agreement when Fenn's data are corrected for drying, which he considers has occurred in his nerves (201, 204). The findings of Gerard (253) on temporaria and esculenta have been duplicated by Schmitt and Meyerhof (537, 650). Table 4 summarizes all the data on active respiration of nerve.

The oxygen consumption to be expected from the heat production of activity is 48 cu. mm. per gram and hour (temporaria, 15°C., 280 shocks per second, intermittent stimulation), and under as nearly as possible identical conditions, but using frogs at a different time of year, the observed average value was 61. This essential agreement in magnitude is paralleled by a similar agreement in time relations, for a large amount of the oxygen consumption, as with the heat production, is delayed for a considerable time, 15 minutes or more, after conduction has ceased. It is important in comparing these sets of measurements to note that heat determinations were made by means of brief tetani, with long intervening rest periods, and the figure cited for respiration was likewise obtained with intermittent tetani lasting 20 seconds, repeated every 4 minutes. When, instead of intermittent, continuous stimulation is used, the respiration per unit time of stimulation is decreased to about one-fourth, although, of course, the total per hour is further increased. The nerve thus shows, as regards its oxygen consumption, a falling to an equilibrium level, or equilibration, quite analogous to that of the heat production. Also, the active increases in respiration in nerves of different species of frog are, absolutely, almost alike, although when expressed as a percentage change of considerably different resting rates, the figures show wide variation. The temperature coefficient of the active respiration is 2.1 from 15° to 25°C. (253)—a value close to that for resting respiration and to that of the absolutely refractory period after conduction of an impulse (240).

Based primarily on a consideration of such differences in percentage increase obtained by several workers, Winterstein (775, 771) has called into question the significance of the increased respiration of nerve consequent to electrical stimulation. (Earlier, he accepted the usual inter-

TABLE 4

Excess oxygen consumption on stimulation

ANIMAL	NERVE	SEASON	TEMPERATURE	OXYGEN CONSUMPTION		OBSERVER	DATE	REFERENCE	METHOD	STIMULATION PER SECOND	REMARKS
				Average	Extremes						
				cmm. per gram and hour	*cmm. per gram and hour*						
Frog:											
Temporaria	Sciatic		?	0		Buytendijk	1910	104–105	O_2—Winkler		
			19–24	+		Haberlandt	1911	700	O_2—volum.		
			22	<80		Adam	1921	7	O_2—manom.		
		Winter	14	48	40–68	Downing, Gerard and Hill	1926	151	Heat	280	Values may be 20 per cent low from standing
			19	34		Gerard, Hill and Zotterman	1927	271	Heat	100	
		Winter	15.2	13.5		Meyerhof and Schmitt	1929	537	O_2—manom.	100 M & B	
Esculenta	Sciatic	Winter	14.6	18.0	11–27	Gerard	1927	253	O_2—manom.	280-contin.	
		Winter	14.6	61.0	48–91	Gerard	1927	253	O_2—manom.	280-intermittent	
		Autumn	15	12		Schmitt	1929	650	O_2—manom.	100?	
Pipiens	Sciatic		21	320		Tashiro	1913	694	CO_2—Ca ppt.		Calc. for R.Q. = 0.8
			19	0		Moore	1919	551	CO_2—color.		Calc. for R.Q. = 0.8
			?	5,300		Sheaff	1922	665	O_2—chem.		

			22	18		Fenn	1927	201	O_2—volum.	100	Corrected to vol. at 0°. Weak stim. = strong
			22	20		Fenn	1927	201	O_2—volum.	200	Corrected to vol. at 0°. Weak stim. = strong
			22	15		Gerard	1930	260	O_2—manom.		Weak stim. = strong
Grylio	Sciatic		22	20		Parker	1925	587	CO_2—color.		
Toad	Sciatic			+		Yamazaki	1927	790	CO_2—Ca ppt.		
Dogfish	Lateral line		23	15		Parker	1925	585	CO_2—color.		Corrected by 1928 results. Calc. for R.Q. = 0.8
			22	11.5		Fenn	1927	199	O_2—volum.	100	Corrected to vol. at 0°
Spider crab	Claw		15	345		Tashiro	1913	694	CO_2—Ca ppt.		Calc. for R.Q. = 0.8
			16	230		Meyerhof and Schultz	1929	538	O_2—manom.	100	Marked fatigue 10>> 100 per impulse
			16	110		Meyerhof and Schultz	1929	538	O_2—manom.	10	
			13	600		Hill	1929	349	Heat	200	Freq. 140–260 same response
Lobster	Ganglion chain		23	49		Parker	1925	586	CO_2—color.		Corrected by 1928 results. Calc. for R.Q. = 0.8
Fish	Trigeminal		?	45		Buytendijk	1910	104–105	O_2—Winkler		

pretations. Thus, he commented upon the failure of one experimenter to obtain an increased carbon dioxide production during nerve activity, ". . . so dass die functionelle Tätigkeit des Nerven nach ihm nicht von Prozessen abhängen würde, die mit CO_2-production einhergehen-zweifellos unrichtige Versuchsergebnisse" 767, p. 385.) In some of Parker's experiments (587), in which the stimulating electrodes and nerve ends lying on them were excluded from the respiratory chamber proper, increases of the order of 25 per cent of the resting metabolism were obtained, whereas in Gerard's (253) experiments, where stimulation occurred within the measuring chamber, increases up to 400 per cent resulted. The greater increase in the latter case, Winterstein suggests, is due to an increased respiration of stimulation under the local influence of the applied currents and is quite independent of the natural conducted process in nerve fibres. His own experiments (770), in which nerve was stimulated within or without the chamber, showed an increased respiration only in the former case. The absolute excess oxygen consumption of nerve, however, as determined by Parker stimulating outside and Gerard stimulating within, was practically the same when continuous tetanization was used in both cases. The much higher percentage increase obtained by me did not depend, therefore, on greater oxygen consumption as a result of stimulation (except in so far as a more active physiological response was obtained and equilibration avoided when intermittent stimulation was used), but rather on a lower resting respiration in the European frog nerves. It has further been found by Fenn (201, 204) and Gerard (253) that after the stimulating shock strength has been increased to give maximum action currents, further increase over a considerable range is not accompanied by still greater respiration, and also (201) that with the nerve killed locally by concentrated saline on the electrode, no increase accompanies strong stimulation.

Special control experiments designed to test any possible effect of the local stimulus in increasing respiration have been performed by Gerard, and Chang (253, 260), and by Meyerhof and Schultz (539). In the former case the nerve was placed on the electrodes in the chamber on one side of a differential manometer, as usual. On the other side only a few millimeters of the ends of the nerves were placed on the electrodes, the remainder having been cut off and placed separately in the chamber. Tetanization of the two sides with shocks just over maximal strength led to the ordinary respiratory increase where the nerves were intact and conduction of impulses possible, a negligibly small one where the

usual amount was exposed to current stimulation but conduction through the great bulk of it was abolished. The second type of control was the converse of this. The intact nerves were laid over three pairs of electrodes and stimulation applied either at one or all. In both cases conduction over the entire fibre was possible but the amount of tissue exposed to local stimulation effects varied as three to one. The increased oxygen consumption on tetanization was alike in both series.

Winterstein (772) has urged that these controls are not valid, since they depend on the assumption that the effect of the applied current is limited to the region of nerve on or adjacent to the electrodes. If, however, applied current spread to and affected distal nerve regions, aside from any conducted physiological impulse, then cutting off a large portion of the nerve would decrease the extra respiration by withdrawing it from the action of the applied currents. Also, if currents introduced through one electrode pair have already acted upon the entire nerve length, simultaneous use of three pairs would have no further influence. If such a marked current spread and effectiveness did indeed occur, it should manifest itself equally in the experiments of Parker and Winterstein himself where the stimulated region was outside of the nerve chamber, since current spread to the inner part and the attendant respiratory increase should still occur.

It is entirely gratuitous to assume such a wide spread of applied currents and their artificial local effects. As Adrian pointed out (10, 472), a nerve cannot really respond to a supramaximal stimulus; for when the current strength at an electrode is above maximal, then, at a region of nerve a greater or lesser distance away, the strength must be just maximal and the impulse would automatically arise at this point. Conversely, as the stimulus strength is reduced, the point of origin of the nerve impulse must approach the region immediately on the electrode. With just slightly supramaximal shocks, therefore, the current applied could not reach stimulating intensity at any distance from the electrode region. It has been shown, in fact (75, 76, 50, 316), that the intensity of current in a nerve produced by polarizing through needle electrodes falls off very rapidly with distance from the electrodes. Even with extremely strong currents no effect could be detected over 12 mm. away in frog nerve (316). The greater spread reported by Kato (387) was obtained on toad nerves with much heavier sheaths. It may be concluded, then, that the controls referred to, performed with just supramaximal currents, could not have been influenced by current spread beyond a millimeter or two from the electrodes; and conse-

quently that the extra oxygen consumption evoked by electrical stimulation of nerve is indeed, as regularly supposed, an index of the conduction process itself. This is further attested by the close parallelism, in magnitude, time course, and change with condition of the nerve, of the active heat production and oxygen consumption; although in the former no question can be raised of current spread and local stimulus complications. Experiments on the Limulus heart ganglion (137) also support this conclusion, since here stimulation of an inhibitory nerve within the chamber leads to an actual diminution of oxygen consumed, though the usual local effects of excitation are all present.

b. *Conduction of natural and artificial impulses. The all-or-nothing law.* It is necessary to consider at this point a more fundamental issue, raised by several workers (726, 719, 782), concerning the identity of impulses evoked by electrical stimulation, tonic or trophic processes, and normal activity of end organs or synapses. This seems to be involved in the distinction Winterstein draws between "stimulus" conduction and "excitation" conduction (769); meaning by the first a transmission of stimulating action by the tissue itself and not the simple physical spread of the exciting agent, such as of applied currents. Of course, a non-identity is hardly compatible with the all-or-nothing principle (nor with present theories of propagation, invoking an electrical excitation of resting via active regions), but this also has been the subject of numerous attacks (382, 169, 495, 50, 765, 784, 641, 783). The great bulk of experimental evidence, however, continues to support this important generalization in the case of vertebrate nerve (387, 139, 388, 621, 494, 732, 14, 713); and even in muscle, where contraction can be elicited in graded fashion (211, 249, 609), it is probable that conduction is all-or-nothing (250, 610). I must limit discussion of the conflicting material to some of the more insistently urged evidence against this principle.

The findings of Mansfeld and his co-workers (495, 496) have been so interpreted. On tetanizing the chorda tympani nerve in dogs for several hours with threshold or strong stimuli, they observed the histological signs of weak or intense secretory activity, respectively, in *all* acini. This appears to rule out the participation of varying numbers of nerve and secretory units (which easily accounts for the varying contractions of a whole muscle); and controls with partly sectioned nerves showed that the individual nerve fibres innervate definite groups of acini. The conclusion is reached that with both strong and weak stimuli at the same frequency the acini are receiving equal numbers of

impulses; in which case the varying response must be consequent to differences in the intensity of the individual nerve impulses in the same nerve fibre. It must be pointed out, however, that there is every reason to believe that the frequencies of impulses with strong and with weak stimulation are not identical. The important factor of equilibration (253, 207, 85) has not been considered. With continued tetanization the nerve irritability falls (85), so that initially threshold shocks become subliminal. (The conduction velocity may be diminished over one-third, 505.) The refractory period is markedly prolonged (207) and, when weak stimuli elicit responses only at each second, third or greater interval of application because they encounter the relatively refractory period, strong ones may continue to be uniformly effective (268, 269).

The secretory response in these experiments, therefore, probably varies with strength of stimulus applied to the nerve by virtue of varying frequencies of impulses set up. The situation would then be entirely analogous to the findings on end organs, which accurately mirror the intensity of stimulus in the frequency of nerve discharge (512, 11, 97). The "iterative" character of vagal activity has been analyzed along similar lines (286), and the situation even in invertebrate nerve-muscle preparations may fall in line (79). Recent work in Adrian's laboratory (713) confirms for the single fibre the older observation that a nerve impulse depressed locally by a narcotic regains full strength upon passing on into a normal stretch of nerve.

A direct experiment (304) to test the identity of "natural" and "artificial" nerve impulses also shows them to be the same. Contractions of the diaphragm induced by electrical stimulation of a sectioned phrenic were compared with those resulting from central discharge down the intact nerve. As both nerves were subjected to various depressing treatments in their peripheral portions, the contractions decreased, disappeared or returned together, so that impulses produced by either form of excitation behaved alike in the nerve trunk. Further, normal respiratory movements can be exactly simulated by proper electrical stimulation of the phrenic nerve (93), and the action potentials led from these nerves on spontaneous or applied excitation are identical (238, 15). The evidence from studies on end organs (511, 14) likewise demonstrates that the afferent impulses set up by their normal excitation cannot be distinguished from those produced by direct stimulation of the nerve trunk, even when studied in the individual fibre by all criteria available.

In the case of the isolated frog cord, it has been reported from Winter-

stein's laboratory (442) that respiration is increased by direct electrical stimulation in rough proportion to the stimulus strength, whereas reflex excitation has no effect. After strychninization, the graded increase on direct stimulation is about the same, but now a small increase appears with reflex activity, and this is independent of shock strength. The irregular and falling resting values and the almost invariable sequence of stimulating the sciatic early and the cord itself late in the experiment, when resting values are low, make the evaluation of these results uncertain. It is not surprising, however, that stimulation via a nerve gives no observable change before strychninization and a small but all-or-nothing increase after this. Under the former conditions, but a small part of the nerve elements are affected, and of these many are acted upon in the sense of inhibition. After strychnine, more elements are reached, though some inhibition is still produced (87, 456, 229). Since the varied stimuli applied to the nerve were all fairly strong, an all-or-nothing response is to be expected. Direct stimulation of the cord, on the contrary, would hardly be all-or-nothing. The number of elements directly excited by the current would, of course, increase with its greater intensity and spread. There is no assurance, even, that neuroglia and other non-nervous tissue were not also involved; and, with the very strong shocks used (up to 5 cm. secondary distance, where 15 cm. gave maximal responses of the nerve), local injury and electrolysis would readily account for marked respiratory changes. The protocols do commonly show, in fact, a marked fall in the *resting* rate following such vigorous treatment. In a later paper (443), the increased respiration following reflex stimulation in the strychninized preparation was no longer found, whereas direct excitation gave increases long after irritability had been lost. A loss of reflex irritability does not, of course, indicate inability of many nerve or other elements to give individual responses to direct stimulation; but after cyanide, moderate local excitation led to no enhanced gas exchange, which is in accord with this comment.

I do not wish to defend the view that in the central nervous system all processes are all-or-nothing—the facts are probably otherwise. Also, in a nerve, the local action of electrical currents must lead to graded chemical changes associated with excitation or injury. This does not appear to be ground, however, for attributing to nerve-fibre conduction, within or outside central masses, any special qualities. So long as impulses pass along fibres, their nature and behavior appear to be un-

influenced by the magnitude of the stimulus that successfully[1] initiated them or its quality as a "natural" or "artificial" one. That other influences than the typical nerve impulse may pass along nerve fibres, as often urged, cannot be excluded by negative results; but if such exist they are surely quite distinct from the usual propagated activity.

3. *Respiratory quotient.* The R.Q. of the extra metabolism of activity is definitely higher than that of rest. All workers agree that the increase is about 0.2, though the absolute values obtained differ considerably. The discusson of methods in connection with the resting quotient applies equally well to the active ones. The actual average values are: 0.97 (253); 0.79 (or 0.87; 537); and 0.77 (or 1.19; 200, 204). It is a striking instance of the difficulty of interpreting R.Q. values that at rest nerve burns relatively large amounts of carbohydrate, while its active metabolism is not associated with any further decrease of the usual carbohydrate fractions. The true significance of the higher R.Q. value is not apparent, though it might be referred to a final oxidation to carbon dioxide during activity of partially oxidized intermediates supplied by the resting processes.

4. *Intermediate processes.* a. *Carbohydrate.* Companion nerves at rest or stimulated in oxygen show the same changes in carbohydrate. Glycogen is not affected in either, nor is lactic acid. The "free sugar" fraction falls progressively in both alike—at a constant rate in bullfrog nerve, at a diminishing one in rabbit (368). There remains a possibility that other carbohydrate moieties, especially the galactose of cerebrosides, are attacked, but no evidence for this has been presented. In the frog nerve, the sugar disappearing in unit time could not be completely oxidized by the resting oxygen consumption, but could be easily by the sum of resting and active. It has been suggested that, at rest, much of the sugar is partially oxidized—enough to destroy its reducing properties. If the oxidation of these products were then completed during activity (in the late recovery phase), the higher R.Q. of the latter would be accounted for. Such a relation of resting to acting metabolism is not *a priori*, very probable, since nerves at rest should then accumulate ever greater amounts of the intermediates (except as removed in the

[1] The possibility of decremental conduction, over limited distances, of impulses only "semi-successfully" initiated, has been demonstrated on the iron wire (459). Such fading excitation waves might be present in muscle (250) or nerve, and may be likened to the travel of a dying spark along a match. The flame of a really "lit" match, on the contrary, travels in a non-decremental, all-or-nothing fashion.

blood stream). Still, if there is no undiscovered error in the results for the frog nerve, this is just what happens in the isolated tissue, cut off rom its blood supply and ganglion cells.

b. *Ammonia and Nucleotide.* It is doubtful how much quantitative reliance may be placed upon ammonia studies in nerve. Expressed as milligrams per cent per hour, Tashiro (697) found, by a colorimetric method, and using quarter-hour intervals, the ammonia given off from resting nerve 2 or more, from active, 4. Winterstein and Hirschberg (773), using the same method, found over an eight-hour period 0.6, for successive four-hour periods 0.9 and 0.3, with the nerves in saline; and larger values in air. The increase on tetanization in saline was 0.6; in air 1.4. Gerard and Meyerhof (275) determined ammonia in the nerve as well as that given off, using aeration and Nesslerization. The fresh nerve contained widely variable amounts, 1 to 5 mgm. per cent, averaging 2.5. During twenty hours the hourly increase in oxygen was 0.2, in nitrogen 0.3. During tetanization for 5 hours, the hourly excess production was 0.45. Gerard and Wen (281) used the excellent Parnas method, (596) which controls demonstrated is accurate with 5 per cent in determining 1μ gram of ammonia, but were unable to obtain consistent results on R. pipiens nerves. The average content of fresh nerve in 67 determinations was 4.0, but this shifted from 5.4 at the end of July to 1.4 in the middle of August, and with large jumps from one experiment to another. A "traumatic" ammonia production (596) could not be established. The hourly formation of ammonia in oxygen at 24° averaged 0.5, in nitrogen 0.3; and the rate was rather more over an eight-hour period than over one of two hours. Individual experiments gave increases of zero to 1.2, which variability is hardly surprising in the face of the large and inconstant initial values and the necessary comparison of two sets of nerves. It is not safe, however, to determine only the ammonia that leaves the nerve, omitting the tissue itself, since much may be lost or retained by it. The excess production on stimulation (5 hours, 24°), averaged 0.3.

Considering all data, it may be taken as a rough average that at rest in oxygen or nitrogen at 20° a nerve forms 0.3–0.4 mgm. per cent per hour and, when stimulated, an extra 0.4–0.5. This very small quantity, compared to other chemical changes occurring, is of no energetic significance in itself. If, however, it signalizes the deaminization and complete oxidation of protein, this would correspond to a breakdown of over 2 mgm. per cent of the latter; which would yield fairly closely the observed heat production and respiration of activity. It is very doubt-

ful, however, if this agreement is more than fortuitous. During rest, ammonia production in the absence of oxygen is as great as in its presence, although during an anoxia of eight or more hours' duration protein oxidation by means of oxidizing reserves must have been suspended. The anaerobic ammonia production, however, continues for a day or more. Narcosis, on the contrary, is claimed to stop its formation (773).

Although the source of this ammonia at rest or activity remains uncertain, it seems entirely possible that it is, as in muscle (181, 176), initially adenylpyrophosphate. This substance has been demonstrated in brain (608) and forms ammonia in the retina when this is stimulated by light (633, 632); and pyrophosphate (280, 279) and pentose (367) have been found in nerve. Ultimately, of course, in a balanced system, ammonia from other sources must help reform the adenylic complex. The aerobic resynthesis of adenylic acid from inosinic acid in muscle seems to depend on ammonia deriving from deaminization of amino acids associated with their oxidation (594). (This must be true, aside from any reversible breakdown and reformation with its own ammonia (176, 595, 177), to whatever extent the originally freed ammonia leaves the tissue.) Work in progress may show to what extent a nerve in oxygen or nitrogen is in equilibrium as regards nucleotide breakdown.

If all the ammonia in fresh nerve, 4 mgm. per cent, were formed from adenylpyrophosphate, there should have been present 14 mgm. per cent of pyrophosphate phosphorus, or about three times the actual amount (279). The resting formation of ammonia would correspond to the breakdown of 1+ mgm. per cent of pyrophosphate phosphorus per hour, the active increase to 1.5. (Adenylpyrophosphate splits off ammonia and orthophosphate along roughly parallel curves, 528, 470, 44, and possibly pentose as well, 179). If all change in the acid stable phosphate fraction of nerve be attributed to pyrophosphate breakdown, this would amount to 0.5 mgm. per cent per hour during rest in nitrogen (complete in five hours), 1.2 during activity in oxygen (for two hours, 280). Actual data on pyrophosphate changes in anoxia (279) show a change close to 1.0 mgm. per cent per hour. The values are obviously of the proper order, though the data compared were obtained under rather different conditions. To the extent that ammonia is produced in larger amounts and for longer periods than accounted for by the nucleotide breakdown, the other sources must be invoked.

Aside from serving as a source of small amounts of ammonia and energy, the adenyl triphosphate may play an important catalytic rôle.

In muscle, at least, it or a closely related substance acts as a coenzyme in glycolysis (528, 471, 190 and 557, 572) and leads to hexose phosphate formation (444, 44). Similarly in erythrocytes, the phosphate content and glycolysis are intimately related (186, 185, 42), and in washed muscle the adenylic complex restores dehydrogenations (312). A possible intermediate position in the chemical machinery between phosphagen and lactic acid has been mentioned. The complex also has a marked pharmacologic action on the heart (153, 154) and may be responsible for some of the effects obtained with central nervous system extracts (427, 617). Further, since magnesium is an esssential for glycolysis, along with enzyme and coenzyme (471), some of the effects of this ion on the activity of the nervous system might be directly related to the action of this nucleotide.

c. *Phosphorus.* Prolonged tetanization of nerve leads to a breakdown of combined phosphate which is progressive over several hours (280). There are two fractions of bound phosphate, an acid-labile, behaving like phosphocreatin, and an acid-stable, containing, probably, adenylpyrophosphate and one or more hexose phosphates. Both contribute phosphate ion to the inorganic fraction, representing the breakdown, particularly, of phosphagen and adenyl triphosphate. Following activity, during aerobic recovery, the phosphate distribution returns toward its original condition. The absolute amount of phosphate extractable from nerve by trichloracetic acid, however, increases with stimulation and remains high after recovery. The additional phosphate appears in the inorganic fraction. Since the known phosphorus compounds present, except the phospholipins and phosphoproteins, are originally extracted in the acid-soluble fraction, the increase in this soluble phosphate must be at the expense of either protein or lipin combinations. Of these, the latter are so strikingly abundant in nerve that it might fairly be assumed that they are the source of the extra phosphate. (The presence of lecithinase in brain, 575, 682, and the spontaneous oxidation of cord lipins, 672, will be recalled in this connection.) The breakdown of phospholipins, so adduced, might be an index of their oxidation, to which in fact other evidence also points; but since the soluble phosphate increases under asphyxial conditions as well, this is not a necessary conclusion.

d. *Creatin phosphate.* A breakdown of creatin phosphate in nerve during activity has been inferred from decreases in the labile phosphate and the bound creatin fractions, which are in quantitative agreement. Only a small part of the phosphocreatin can be broken down by teta-

nization continued for hours, at frequencies well into the relatively refractory period. Splitting is at first comparatively rapid, then less, and after two hours, at the outside, no further shift in the equilibrium value occurs. Resynthesis occurs during rest in oxygen following a period of activity, but there is no evidence for a rapid reformation during the first few seconds after tetanization has stopped, as described for muscle (558, 294), since the phosphagen content of nerves frozen in liquid air during tetanization is no lower than those examined some minutes later (280). The possibility of course exists that during actual conduction a considerably greater breakdown occurs, to be reversed during the refractory period. The shift in the balance after continued tetanization would then represent only the altered physiological state of the rested and "fatigued" nerve, and so be a further index of equilibration.

A nerve tetanized in nitrogen loses phosphocreatin more rapidly than one at rest, during the few hours that conduction is retained (279). This might be interpreted as favoring the normal existence of a rapid breakdown during activity and a subsequent rapid restoration with the aid of oxidations. In the presence of iodoacetic acid, stimulation in nitrogen leads to a greater breakdown than occurs in the untreated nerve under similar conditions. Since nerve produces lactic acid during anoxia, which process is largely abolished by the halide, it would appear that the energy from glycolysis as well as respiration may be utilized for phosphocreatin resynthesis. In muscle, however, iodoacetate also interferes with the utilization of oxidation energy (111), so that this result might, improbably, represent interference with the use of the oxidizing reserve. It will be necessary to return later to a consideration of these points.

In fresh lobster nerve, there is an average of 42 mgm. per cent acid soluble phosphorus, of which 12 mgm. per cent is in the stable fraction and 5 mgm. per cent as phosphagen (behaving like arginine phosphate). During two hours' anoxia, about one-fourth of the stable and two-thirds of the phosphagen fractions break down (693).

B. *Anoxic Behavior.* 1. *Heat production.* The extra heat production of nerve tetanized in the absence of oxygen or under the influence of cyanide falls progressively for two to three hours to zero. During this period, however, in sharp contrast to muscle, the delayed phase is retained. The ratio of initial to delayed heat is certainly not increased and some evidence has been presented (255) that it is actually diminished. It is a striking fact that, although the heat production depends

certainly on the ultimate completion of oxidations, neither phase is directly abolished by oxygen lack. This is strikingly different from muscle, which utilizes an intermediate lactic acid mechanism to obtain anaerobic energy by borrowing on future oxidations. It is worth noting further that the ratio of anaerobic to aerobic heat in muscle is just under one and that of total initial to total delayed is 1 to 1.5. In nerve the ratio is 1 to 9 or more, and if a lactic acid mechanism were involved, this would require the complete oxidation during the delayed phase of all lactic acid formed during the initial one. In the crab nerve, in fact, delayed heat production is 98 per cent of the whole, which at once eliminates even such a possibility (349). That a lactic acid cycle is not involved in nerve activity is further shown by direct study of this substance. During anoxia, lactic acid increases continually in resting nerve, but the rate and amount of its production are entirely unaffected by activity (275, 367).

2. *Gas exchange.* During rest in nitrogen a nerve continues to produce carbon dioxide and develop an oxygen debt, as measured by an extra oxygen consumption when this gas is readmitted. A nerve tetanized in absence of oxygen develops a greater debt than its resting companion (253, 650), but the anaerobic carbon dioxide production is not increased (201, 204, 650). Again the evidence leads to a suggestion of incomplete oxidations. Thus, for example, if lipins are the main or only fuel of activity, oxidation at double bonds in the fatty acids would yield as a first product poly-hydroxyacids (674). Such a reaction would use oxygen but lead to no carbon dioxide production until the oxidations were completed. It has been stated that lecithin is oxidized by air in the presence of metal traces (706, 753, 735, 626) with no production of carbon dioxide. (This oxidation is especially catalysed by hemins not acting by a reverable valence change, 786, and is not sensitive to cyanide, 626, 428, 787. But see 420.) The oxygen consumed corresponds well with the theoretical amount needed to oxidize two of the three double bonds of linolenic acid to the hydroxy derivatives (724), and it is further known (428) that a single double bond oxidizes only one-hundredth as rapidly as do three, which is in accord with this incomplete oxidation. It is hoped that studies on nerve lipins now in progress will decide to what extent these are normally oxidized in nerve and what rôle they may play during its activity in nitrogen.

The questions must further be considered: first, how is nerve activity maintained for hours in the absence of a supply of oxygen; and second, what is the cause of its ultimate failure. Since conduction depends on

the activability of nerve, which is a function of its resting condition, this will be possible only so long as the resting nerve has not undergone more than a critical amount of change. Maintenance will depend, then, on the availability of energy for the resting as well as the active requirements. For the latter there have been described two possible sources, continued oxidations at the expense of an oxidizing reserve, and breakdown of phosphocreatin; for the resting, in addition to these, the energy of glycolysis. It may be well at this point to distinguish between an oxidizing reserve and an energy reserve.

3. *Energy and oxidizing reserves.* As discussed, a given amount of oxidation may occur with widely varying energy liberation, and also energy can be obtained from reactions not directly related to oxygen or carbon dioxide changes. The existence in nerve of phosphocreatin and of sugar, able to break down respectively to free phosphate and creatin and to lactic acid, makes possible continued energy liberation, therefore an energy reserve, independently of an oxidizing one. On the other hand, a considerable oxidizing reserve may be but a small source of energy. It will be recalled that the main liberation of energy during oxidations is associated with the reduction of the oxygen itself, that only small energy changes are involved in oxido-reduction of reversible systems, and that the final substrate oxidation actually requires application of energy. If one or several intermediate reversible systems are interposed between substrate and oxygen, the bulk of energy must be freed when the gas oxidizes the first of these. (To the extent that the intermediates carry oxygen as peroxide, rather than being oxidized by it and later serving in turn as oxidizers, this does not hold. The peroxide systems of tissues may be, for this reason, of considerably more importance than often supposed. Compare 664 on induced oxidations by peroxide formed during glucose oxidation by O_2.) Oxidized intermediates would then constitute an oxidizing reserve, but not a liberal source of energy.

Parenthetically, if this reasoning be correct, a large fraction of the energy utilized by the cell must be "captured" by the machinery at this initial step of oxidations. Since the catalysts appear to be intimately related to structural surfaces (734, 754, 736), and since also the cell machinery for routing free energy to useful ends seems to be largely a structural one (733, 734, 526, 53, 527, 741, 257, 350), this conclusion does not appear improbable. (It is interesting, for example, that catalytic reactions often yield asymmetric products *in vivo*, while the extracted enzymes give racemates—e.g., glyoxalase, 135.) The substrate ulti-

mately oxidized then fades in importance to the rôle of "oxygen acceptor," in the same sense as oxygen or methylene blue have been regarded as serving passively as hydrogen acceptors, and is necessary only to remove end products of the really significant reaction.

To return to the questions regarding nerve asphyxia, it seems reasonable that conduction can persist as long as: 1, the physico-chemical state of the resting nerve (membrane condition especially) is able to undergo the changes essential to conduction, a continuous "resting" energy liberation being required for this; 2, the energy necessary for conduction and restoration is available; and 3, the catalytic and other mechanisms required for its traffic are able to function.

When the resting potential of nerve falls only 1–2 millivolts, a small fraction of its total value, conduction is largely blocked. This is true not only for asphyxia (257) but also for potassium chloride, veratrine, aconitine, etc. (74). After withdrawal of oxygen, the oxidizing and other energy stores are tapped to maintain the resting equilibrium, as well as for activity. If more activity is elicited, the total reserve will be sooner exhausted (701); or, for the same amount of activity, if part of the total reserve is excluded—as is the formation of lactic acid by iodoacetate (629)—block will result earlier. This assumes that, at least in part, the resting and active needs can be met from common energy sources. This seems certainly true for phosphocreatin, which breaks down both during rest in the absence of oxygen and during conduction even in its presence; and probably is also true for the oxidizing reserve, although this is used in different reactions during rest and activity. The lactic mechanism, according to all evidence yet available, can contribute only to the resting needs; yet if made unavailable must none the less hasten loss of conduction. It is significant in this connection that methylene blue accelerates the resting but not the active respiration of nerve (260); although, at least for central nervous tissue, the dye reduction is hastened during activity (352, 397).

There is no *a priori* reason why asphyxia of nerve may not be prevented, or an asphyxiated nerve restored, by other agents than oxygen. Any substance that is able to serve as hydrogen acceptor in the given chemical system and which yields sufficient energy upon reduction should act in a similar manner. Experiments with methylene blue (Feng and Gerard, 195, 259, confirmed by Schmitt and Schmitt, 656) yielded negative results. Since the anoxic nerve does reduce the dye, this failure cannot mean lack of reaction. Either, then, methylene blue enters into the usual reactions in insufficient quantity or enters into

different reactions or, in either case, does not yield sufficient energy on reduction. Since the dye increases respiration in the presence of oxygen, the first possibility is unlikely, and recent evidence on its action (*vide supra*) indicates that it enters into the usual catalytic system.

The non-effectiveness of methylene blue appears, thus, to be related to the paucity of its reduction energy; and greater success might be expected from a substance with a greater yield. Metadinitrobenzene, introduced as a hydrogen acceptor by Lipschitz (463, 462), is such a reagent. Its heat of reduction to m-nitrophenylhydroxylamine is (from data in 401) 71 kil. cal. per mole, or, per electron pair, 35.5. Reduction of oxygen ($O_2/2$) to water yields 68.4, and of methylene blue to white 25.7 (524). (Meyerhof's figure for the dye reduction has been criticized on thermodynamic grounds, 120, and a somewhat lower value deduced from potential data.) Using this substance in place of methylene blue, Cohen and Gerard (121) have obtained definite recovery of conduction in an asphyxiated nerve; but since the conditions of its action are not yet clear and most experiments have been unsuccessful, we cannot make a final report on its effectiveness. $NaNO_2$ has yielded more consistently positive results. Lipschitz and Hertwig (464) were able to restore the motility of asphyxiated spermatozoa in a similar manner. This agent, moreover, does not act upon the respiration system as does methylene blue, since it has little or no effect on oxygen consumption nor on the inhibition produced by cyanide (115). It also fails to affect phosphocreatin in nerves at rest in oxygen or nitrogen (279).

It is worth noting that, in oxidizing methyl alcohol to formaldehyde, oxygen liberates 45 cal. and methylene blue only 2.7 cal. (524). The nitro compound should yield 13 cal. under the same conditions, almost a third of that given by oxygen and five times as much as the dye. (For oxygen, $68.4 - 23 = 45.4$; for metadinitrobenzene, $35.5 - 23 = 12.5$; for methylene blue, $25.7 - 23 = 2.7$.) (Compare the oxidation of lactic to pyruvic acid (684), by KNO_3 it gives 30.7 cal., by $\frac{1}{2}$ O_2, 51.9.) Further, per electron pair, more energy must be added to the molecule to oxidize an aldehyde to an acid or split carbon dioxide from the latter than to introduce an oxygen into a hydrocarbon group or change the alcohol to aldehyde (calculated from combustion heats for methane, ethane, propane, ethylene sequences in 401). It is not surprising, then, that whereas oxidations by oxygen tend to run to completion, with carbon dioxide liberation, those by methylene blue or the nitrobenzene often do not (524, 462). A similar situation should obtain in a nerve in nitrogen, maintaining oxidations with a reserve of oxidized

intermediates, and considerably more oxidation may occur than expresses itself in carbon dioxide formation. It is, of course, understood that in any particular case the reaction limits may be set by kinetic rather than energetic factors.

4. *The effect of salts.* The problem of nerve asphyxia is complicated further by the action of saline solutions. It has often been claimed that an asphyxiated nerve recovers partly (and temporarily) when bathed in oxygen-free Ringer (209, 296, 297, 127, 333) and completely only after combined fluid and oxygen. This last point is dubious, for several workers have obtained full recovery of action potential or of contraction of an attached muscle with oxygen alone (34, 226, 257). The partial recovery in Ringer, however, may be accepted—providing the nerve sheath is not acting as a sufficient barrier to diffusion (195).

These observations have been interpreted to mean that during anoxia "toxic" metabolic products accumulate and are directly responsible for block. They are removable in part by out-diffusion into a bathing saline solution, in part by oxidation, but completely only by the combination of both. Lactic acid and other acid intermediates have been more especially invoked in this connection (447). Certainly neither lactate ion nor simple acidity is the critical factor, for an asphyxiated nerve recovers to the same extent in Ringer containing sodium lactate and / or buffered at pH 6 to 9 (195, 196). Further, out-diffusion of any substance is rendered unlikely, for bathing the blocked nerve in several cubic centimeters of Ringer or merely moistening it with a few cubic millimeters will alike give temporary recovery. An apparently crucial result, excluding out-diffusion of any special substance, is obtained by soaking a nerve for half an hour in sodium chloride before beginning the asphyxia. Such a nerve blocks in the same time in anoxia and recovers as well in oxygen as a companion nerve kept for the same period in Ringer. Whereas the latter, however, shows the usual partial recovery when bathed in oxygen-free sodium chloride, the former shows none. That the sodium chloride nerve is not injured is demonstrated by its full recovery in oxygen and also by replacing it in Ringer before the asphyxia, when the sodium chloride effect disappears. Also, it may be added, after eight hours' anoxia even the usual Ringer-treated nerve no longer shows recovery in a saline solution though still regaining almost full activity in oxygen.

The saline is thus seen to act in terms of its ions rather than as a fluid volume into which toxic metabolites can diffuse. It is tempting to relate this effect to reversible inexcitability of muscle (157, 374, 206, 485)

and to the results of the Woronzow school on nerve (779, 781, 565, 603, 718, 37, 756. See also 491). In muscle, the inexcitability seems to result from a redistribution of ions, especially potassium, between intracellular and intercellular fluids and so an alteration of conditions at the surface membranes. When the extra potassium is allowed to diffuse out from the tissue spaces, irritability returns. That such a spontaneous change is not seen in nerve is not surprising, for each fibre is heavily insulated, especially with myelin. An increased membrane permeability to ions as asphyxia proceeds (702, 703, 257. Contrast narcosis, 724, 245) would, however, make such a migration possible, and that excess potassium or calcium applied to nerve fibres from the outside can block conduction is well known (615, 580, 509, 81, 359, 80, 362, 432, 545, 361). This block may be an indirect result of increased membrane permeability and loss of resting polarization (486, 432). In just what way the sodium chloride or Ringer acts during nerve asphyxia remains to be elucidated; but it would be highly interesting to determine if polar currents, especially in combination with salts, could restore conduction in a freshly asphyxiated stretch of nerve. Suggestive results in this direction have been reported (702, 703). A least, for a nerve asphyxiated after Ringer, even 0.1 per cent sodium chloride in sugar leads to some recovery, whereas isotonic sugar does not (195).

It follows, in any event, that the first failure of conduction of a nerve subjected to oxygen lack is not due to the second factor enumerated—lack of available energy. It may depend on the disturbed milieu preventing or retarding the necessary catalytic reactions for liberating this energy or, more likely, on the disturbed resting state. Certainly the resting potential is but slightly depressed at the time block supervenes, though it continues to fall during hours in anoxia, and if this potential is maintained by continual energy expenditure, then such turnover must also continue long after conduction is lost. The block, then, would depend first on disturbed electrolyte balance related to membrane changes, which, in turn, result from lessened energy supply. Later, when saline is no longer able to cause any recovery but oxygen still is, the energy factor may be the more immediately crucial one.

C. *Time Relations.* It has been pointed out that the active energy exchange of nerve, as measured by heat and respiration, outlasts actual conduction by many minutes. The heat liberation, further, occurs in at least two distinct phases, the one approximately associated with conduction (and refractory period), the other following. Action potentials of variable duration, often far beyond the usual sigma or two, have long

been recognized in nerve (235, 709, 237, 780, 71, 268) and seem to change with the state of the tissue. A particularly striking demonstration of these "delayed potentials," "after potentials," "retentions," or "low-voltage elements," as they have been variously called, was obtained by Levin (447) on crab and by Amerson and Downing (23) on frog nerve. These lasted as much as half a minute in the frog after a single impulse; several minutes in the crustacean nerve, after a period of moderate activity. The obvious suggestion from the thermal studies has been pursued in further work, and the late action potential shown, on the one hand, to represent a distinct phase separable from the initial of "spike" potential accompanying the impulse (71, 23, 257, 244, 334, 25, 655), and on the other, to endure for ten minutes or more, (258), as does the delayed heat. These very late potentials are predominantly positive.

It is obviously desirable to relate in time and magnitude the thermal, electrical, metabolic and physical (permeability, etc.) changes attendant on and subsequent to activity of nerves under normal and various experimental conditions. This will be attempted only to a limited extent.

1. *Initial changes.* The initial heat and action potential are surely associated with conduction. This is generally related to membrane changes, both physical and chemical. The most widely applied theory (457, 458) posits a membrane sufficiently impermeable to ions (634; anions, 568, 361) to maintain a resting polarization across it—positive outside, negative within. When some region is in any manner depolarized beyond a critical value, it becomes permeable to ions and permits adjacent regions to depolarize, like a condenser, by means of ion currents flowing through the "leak." These regions then become in turn permeable and so the wave of change spreads. Though a more or less complete breakdown of the membrane is often pictured, this is not a necessity. It is well known that alteration in the charge of a membrane is sufficient to cause great changes in differential permeability (566, 550, 24), so that the mere depolarization might lead to the consequent events in nerve. The greater body of evidence decidedly favors the view that nerve resistances, especially the polarizable resistances, are definitely lowered during conduction (see, e.g., 677, 284, 724, 163, 164, 725, 476; and compare, 634, 567, 251), though some workers question this (407, 71).

A simple physical picture of this kind, however, is surely incomplete, for explosive chemical reactions are also a part of conduction and are

most probably concentrated at membranes. The exact correlation of the intimate physical and chemical events at the axone membrane is a pressing problem awaiting solution. It is not certain, even for the initial or spike action potential, whether this signalizes simply a wave of depolarization passing along the fibre or the actual development of new potentials at the active region, or both. In the first case, the amplitude of the action potential should closely parallel the resting one. Over a considerable range of conditions this is true (61, 231, 257; see 414 on irritability and injury potential), but it seems not always to be so (257, 74). It must be remembered, however, that when a whole nerve rather than a single fibre is being studied, there is the danger of decreased action potential, besides any in the individual unit, appearing as an average effect due to entire failure of many units in a statistical fashion. Sheath changes may also affect the two potentials differently. The initial heat is far more than could be accounted for in terms of the electric currents (345) and is the best evidence that some of the observed chemical reactions are in fact associated with conduction itself.

During the refractory period after conduction, the immediate machinery is "reset." This implies a reformation of polarized membrane and of the explosive substance to be set off. Energy is required for this; but whether it is obtained by new energy yielding reactions at this stage or from the amount previously set free during conduction, is not known. There is good reason to consider the initial heat production to contain two phases (271), but no evidence as to how they are related is available. In muscle, examples of both conditions can be found. The anaerobic resynthesis of phosphagen after a contraction (558) is driven forward by the concurrent formation of lactic acid (445, 530, 350, 540, 446), and the anaerobic delayed heat is equal to the difference between that liberated and that stored (350). Here primary recovery involves further energy degradation. On the other hand, there is some evidence that a muscle which has performed mechanical work during contraction can utilize part of the potential energy of the lifted weight to decrease the energy change of subsequent relaxation (197, 198, 346, 789), though later work renders this doubtful (350). There is also much uncertainty of the exact relations between the recovery of excitability (refractory period) (16, 472, 188), of energy-liberating capacity (intensity of impulse) (9, 271), of electric neutrality (fall of the spike current) (240), of conduction velocity (221, 241), and other properties immediately following conduction; though they are all closely related.

2. *Late changes.* The late and prolonged changes after conduction

offer, however, the most difficult problem of interpretation. The large heat production and respiration show that the bulk of energy exchange takes place during this time and is released primarily by oxidations. The other prominent sign of late changes is the after-potential. This has been interpreted in several ways, and the facts are not easily reconciled with any one view. The magnitude of this potential at any moment might correspond to the rate of chemical and membrane change at the time (25) or to the amount of restoration to the resting state still incompleted (231, 244). On either view, the potential should be maximal at the start and fall in a roughly exponential fashion to zero, as it does, since both the rate of recovery and the amount incompleted (total recovery less actual recovery) fall asymptotically to zero. Evidence from heat studies (254) indicates that the recovery is governed by a key reaction which is monomolecular, giving the equation $x = ae^{-kt}$ for the recovery yet to occur and $-\frac{dx}{dt} = kae^{-kt}$ for the rate. Obviously the differential has the same form as the integral.

When, however, the time scale is altered, as by temperature or drugs, or the amount of recovery to be achieved, as by fatigue, anoxia or drugs; then rate and amount of recovery should vary in opposite directions. If the potential amplitude indicates rate, and area quantity, of recovery,—as for the delayed heat production—then one would expect a decreased amplitude and constant area with cold and carbon dioxide, decrease in both (though probably with prolongation, if amplitude falls more than area) in anoxia. Warming should lead to greater amplitude but constant area, fatigue or equilibration to subsequent increase in both. Veratrin, which greatly increases at least the resting oxygen consumption (653), presumably by acting somewhat as persistent cathodal polarization does to keep the membrane from reforming, should also lead to increase in both. All these are, of course, in relation to the amount of initial change, not in absolute values, since recovery is in terms of the amount of change at the end of conduction.

Different workers, using slow or rapid recording systems, have not all obtained concordant results. This may depend, in part, on the emphasis on early or late portions of the late potential; and it is not impossible that the early part, say up to half a second, is of different significance than the remainder, lasting ten minutes. There is general agreement, however, that fatigue (255, 244, 25) acts as indicated above. Cold (244, 25) decreases amplitude and also area. Veratrin also has the expected action (234, 299). Carbon dioxide, however, has the

reverse effect (prediction made on the basis of its slowing reactions, 563, 333, and decreasing respiration, 630) according to all workers (731, 82, 140, 563, 25); and for anoxia there is no agreement. Furusawa (231) and Gerard (257) interpreted their evidence as showing increased after-potential. Amberson, Parpart and Sanders (25) by a more direct method found a decrease, as did Amberson and Gasser (25) with the oscillograph. Heinbecker and Bishop (334), however, report temporary increases and never a decrease, using the same instrument on other nerves. Graham (300) finds an increased amplitude and duration in the presence of excess Ba or Ca, a decrease with excess K. It will be very useful, in resolving the present tangle, to have comparable data on the course and amount of the delayed heat production of nerve under the influence of carbon dioxide (and other chemicals) and at various temperatures, as well as more complete data on the changes during anoxia. Gasser's careful analysis of the influence of temperature on the action potential and related properties of nerve (240) may be recalled in this connection.

It would carry this review too far to discuss the question of positive after-potentials in any detail, nor is there much certain evidence on which to do so. Oscillograph records have led several workers (244, 334) to relegate these to persistent negative after-potentials at the injured end (see also 780). Others (236, 676, 257, 25) have taken them to represent part of the local change at the functional region, particularly because they change with the state of this region, as under carbon dioxide action (676, 563, 25), anoxia (676, 284, 257, 25), or temperature change (236), even when the nerve end is unexposed. If the former view is correct, they are of little further interest; if the latter, it remains to analyze their relations to metabolic and membrane changes. The suggestion that the positive change is a form of "overshoot," like the supernormal phase in irritability, comes to mind, but is hardly an explanation.

3. *Equilibration.* The question of equilibration must be touched briefly in this connection. If recovery of nerve from a few seconds' activity is not complete for many minutes, it might be expected that a second period of activity evoked during this time would differ from the first. After each individual conducted impulse, sufficient return of functional capacity is achieved during the refractory period for another conduction to occur.

This immediate restoration, however, must ultimately depend on the energy of the later reactions; which, with continued activity, lag further behind those of conduction and of prompt resetting of the mechanism.

The latter would then also begin to lag, so that at a given interval between impulses the initial recovery is less complete than at first. This amounts to a prolongation of the refractory period. Also, again at a constant interval greater than the absolutely refractory period, the amount of new breakdown that attends each impulse must also be less, since a smaller store is available. The total late recovery to be completed, on the contrary, becomes greater after continued activity, since an accumulated recovery deficit exists. Finally, these changes should be progressive with continued tetanization, but only in an asymptotic manner; for as the early processes lag more and more, a level is reached at which they no longer exceed the rate of recovery and an equilibrium level is reached. The harder a nerve is driven by strong and frequent stimuli, the longer can breakdown be kept ahead of recovery and the lower the level of equilibration reached. Complete fatigue of a nerve, in the sense of inactivity as an end result of activity alone, is ordinarily impossible because the absolutely refractory period prevents driving it to this extreme. This accounts for the results of the long series of experiments showing the non-fatiguability of nerve.

Such a view of nerve activity leads directly to an expectation of the following changes during equilibration, and of their reversal during rest and recovery—and every one has been verified: decreased heat production per impulse (271, 255); similarly for oxygen consumption (164, 209); increased action potential (244, 25; but see 268); decreased initial potential (268, 222); prolonged refractory period (207, 268); raised threshold (85); slowed conduction (308, 274). Further, decreased functional capacity after activity is more marked at lower temperatures, less at higher (109, 709). It is also more easily attained after strychninization (31).

4. *Mechanisms.* Three separate reactions in series have been assumed in this discussion, without any expression as to their more exact character. Somewhat more specific suggestions on this point were hazarded four years ago (256). Though in several details surely incorrect, the main structure still appears useful as a basis for giving concreteness to the position here developed. The equations were:

(1) During conduction—very rapid: $CA \rightarrow A + X$
(2) During refractory period—moderately rapid: $C + A + E \rightarrow CA$
(3) During the long recovery period—very slow: $X + O_2 \rightarrow CO_2 + E$

It was guessed that CA might be a hexose phosphate; X, an intermediate of carbohydrate breakdown; and E, energy. Though oxidations were

certainly involved in the last reaction, the participations of oxidations (or oxygenations) in the earlier ones was uncertain. This is still an open question, as the experiments with carbon monoxide which Schmitt (652) seemed, at first, to believe gave an affirmative answer, are not conclusive in this direction (651).

More recent results have, however, made it improbable that sugar enters the reaction system and have turned more emphasis to creatin phosphate and adenylpyrophosphate. Oxygen would then hardly be involved in the early changes. The reactions might then be written (264):

$$(1)\ CP \rightarrow C + P\ (+ x)$$
$$(2)\ C + P + E \rightarrow CP$$
$$(3)\ F + O_2\ (+ x) \rightarrow CO_2 + E$$

where CP represents creatin phosphate; E, energy; and F, food. The x here implies only some controlling mechanism which causes reaction (3) to keep pace (or rather follow after—but quantitatively) with (1) and (2). This might even be phosphate, which does accelerate respiration, possibly through changes in ionic calcium (114), or free creatin—though the latter does not affect oxygen consumption (115), and in moderately large concentrations depresses irritability and conduction velocity (599)—or changes in the amount of adenyl triphosphate or its derivatives.

5. *Relation to thermal data.* It is surely too early to attempt to quantitate the chemical with the thermal events in nerve, especially since even for the intensely studied muscle this has been but partly successful. A brief statement of the caloric equivalent of known reactions may, however, prove useful. During a two-hour tetanization, some 5 mgm. per cent of phosphorus is liberated from phosphocreatin, or 0.15 mgm. of phosphoric acid per gram of nerve. Since one gram of this substance breaking down liberates about 160 cal. in muscle (535), this would represent a heat production of 0.025 cal. per gram nerve. (One hundred and twenty calories per gram may be a better figure, 534, to assume, but would not alter the order of the calculations.) A single impulse actually liberates, per gram nerve, 10^{-7} cal. initial or 10^{-6} cal. total heat. For long periods of activity at high frequencies, the heat per second is only some twenty-five times this value, so that per hour activity the total heat would be of the order of 0.1 cal. The phosphagen broken down (in excess of that reformed, of course) might thus about account for the initial heat for two hours. This close agreement is not to be given much weight since,

if creatin phosphate is decomposed during conduction and reformed later, larger amounts should have changed than are actually determined. The heat equivalent of adenylpyrophosphate, when calculated on the assumption, previously made, that acid-stable phosphate changes may be entirely referred to this substance, and using the value 170 cal. per gram phosphate liberated (535), appears to be of secondary importance; for during two hours' tetanization only 0.001 cal. per gram of nerve could result from its breakdown to ammonia, orthophosphate and inosinic acid. (Recent results on pyrophosphate may raise this figure slightly.)

During anoxia the known changes include, besides oxidations, lactic acid production and liberation of phosphorus from phosphagen and the adenylic complex. Taking the highest rate for each of these, respectively, as 7, 3, and 1 mgm. per cent per hour, the energy freed would be 26, 1.5 and 0.5 times 10^{-3} cal., or 0.028 cal. per gram of nerve per hour. At rest in oxygen the energy liberation from oxidations is over 0.1 cal. per hour, so that, aside from energy available from the oxidizing reserve, the nerve in nitrogen has at best one-fourth the energy production rate it normally maintains.

D. *Inhibition.* Throughout the discussion of activity in the nerve fibre, a positive direction has been assumed. There is no evidence to date of any form of activation resulting in lessened activity of nerve. The various forms of Wedensky inhibition all depend, ultimately, on increased activity, leading to block on the basis of a pre-existing differential depression (389, 390, 220). The end effect of a nerve impulse, at an effector end organ or on another nerve cell, however, can be distinctly inhibitory (see 99). In some cases this may depend on some type of interference mechanism, but in others it surely does not. Perhaps most striking are the effects of stimulating inhibitory nerves to the heart ganglion of limulus on the respiration of this nervous tissue. Garrey (233) obtained decreases in carbon dioxide production amounting to 40 per cent, and Dann and Gardner (137) observed a lowering of oxygen consumption of over 70 per cent of the total. It is difficult to see how such a depressed metabolic activity of nerve cells and fibres can be maintained except as a result of the liberation of substances with a depressant action. (If kept low by continued polarization, by action currents, or the like, other regions must keep active to give the potentials. A much smaller amount of activity would suffice on a chemical basis.)

E. *Neuro-humoral Effects.* The above results lead directly to a consideration of another phase of the chemical activity of nerve. The view

has long been entertained that efferent nerves act on the effector organs they innervate through the intermediacy of chemicals, liberated presumably at the end organ. This has been urged more in the case of autonomic fibres and especially for those leading to inhibition. The early work of Howell (376, 377) relating vagal inhibition of the heart to potassium ion will be recalled, as well as the considerable recent evidence that stimulation of the vagus causes to appear in heart perfusion fluid an inhibitor to another heart (469, 91, 791, 92, 776, 617, 184). The behavior of this substance, chemical and pharmacological, has led some to identify it with acetyl choline (e.g., 136) which has been demonstrated in tissues (62). (It cannot escape notice that this is closely related to an end product of phospholipin or myelin breakdown and therefore to be considered in relation with other evidence as to the possible participation of myelin in the active metabolism of nerve.) Other effects of parasympathetic fibre activity, on gut for example (91, but see negative results, 223), are similarly referred to the same substance, as are muscle responses to antidromic impulses (356, 357, 239). A vagal humoral control of gastric and pancreatic juices is also claimed (617). In the autonomic system it has been urged that the specific substance acts in relation to a shift in the K-Ca balance (791, 418), and evidence has been presented that calcium ion must be present for sympathetic, potassium ion for parasympathetic nerve stimulation to be effective (e.g., 710).

Histamine has also been found in fresh tissues (252, 62, 63), and this or a related substance shown to contribute to vasomotor reactions. Thus, Lewis and his co-workers (450, 451, 452) offer evidence that local reddening and vesiculation of the skin after a variety of stimulations or injuries and in herpes zoster depend on liberation of such a vasodilatant (but see 318, 490). Cannon and Bacq (108) have recently demonstrated the liberation in smooth muscle, in physiologically effective amounts, of a substance, seemingly epinephrine, when the sympathetic is stimulated. Humoral control of melanophores via the nerve has been shown (598, 592). Haberlandt (311) has found a marked stimulating action produced by feeding dialysed brain extracts, and it is claimed (427) that a perfusate of resting dog brain enhances the rabbit heart beat, whereas one from a stimulated brain is toxic to the heart. Other extracts causing cardiac or smooth muscle changes have been obtained (381). The alcohol extract of nerve is reported to produce a vagal-like action on the heart (776, 617), and the claim that the presence of a degenerating sciatic affects the irritability of the intact one will be recalled (4).

In the nervous system itself, a similar mechanism has been considered by several workers (659, 317, 474, 58, 640, 669, 229, 642, 265, 167). The end of an axone is at least an unspecialized end organ, often a complicated one (as, for example, in the olfactory glomeruli, 340, p. 253) and might activate the dendrite or cell body on which it impinges via chemical as well as electrical changes. The transmission from cell to cell by means of action potentials has long been the orthodox view, and emphasis on the chemical possibilities has had a novel flavor. In fact, however, the conduction along a nerve fibre involves excitation of a resting region by an active one, and both electrical and chemical components are present in the mechanism of propagation. At the ending, which is specialized, at least anatomically, either or both components might well be exaggerated to facilitate transmission over a critical region. Long-enduring action or depolarization potentials or special chemical accumulation might equally well be utilized in various situations and (except for familiarity with the one idea) one seems as likely as the other. One interesting analysis of junctional transmission has been made in terms of long-enduring excitation states (88), and it is significant that the theory of isochronism appears to be breaking down (637, 434, 305).

Certainly the concept of a central excitatory or inhibitory state (669), which so happily harmonizes much of our knowledge of the behavior of the central nervous system, is easily concretized in chemical terms. Eccles and Sherrington (167) have recently rather turned from such a chemical interpretation because of difficulties in the speed of action (see also 219, 220, 168). Quantities of substance liberated by separate axones in two dendrites could lead to summated effects only by diffusing to a region of common action. But diffusion would carry the great bulk of the substance to the cell interior, while activity probably depends on the surface membrane. Also, such interior material could not be promptly used up by a surface response (or liberation of opposing stuff) and should manifest itself later by diffusing in turn to the surface.

The difficulties considered are very real—though for diffusion over dimensions measured in micra, times in sigma would suffice—but are possibly even more serious when potentials rather than chemicals are considered to represent these cell states. Since impulses reaching spatially separated dendrites of a single motoneuron do summate in producing motor discharges, there must be some common locus of action; and some agent must carry the separate changes to this region. If a potential change sweeping along surfaces and leaving a relatively lasting diminution in polarization is imagined, a picture not unlike

conduction in the nerve fibre emerges. But a similar, if inverse, change must be assumed to follow the arrival of an inhibitory impulse. This appears to require a second, qualitatively different, membrane change propagating along the same membrane as the excitatory one, and leading to opposite polarization effects. Though not inconceivable, such a system certainly has no known prototype and is not very attractive. (A more encouraging situation would result if there existed a spacial separation of excitatory and inhibitory endings on opposite poles of a motoneurone. The same local change in each group might lead in one case to increase, in the other to decrease, of a pre-existing polarization or other gradient along the cell, and so its state of activity. Adrian's study of the isolated nervous system of the water beetle (13) shows spontaneous, slow and rhythmic changes in the potential difference between ganglion cells and their axones. This, however, he considers as a consequence of changes in the central excitatory state rather than as the state itself.) A chemical mechanism and diffusion would not lead to such a difficulty, and it is tempting to consider here specific possibilities.

The antagonism of hydrogen and hydroxyl ions, still more of potassium and calcium, on the activity of nerve fibres and cells has been exhaustively studied. *In vivo,* as well as *in vitro,* unbalance of the normal ratios is associated with relatively long-lasting states of overactivity and actual motor discharge (parathyroid tetany, 484, 638, 602), or underactivity and coma or sleep (calcium or magnesium excess, 122, 519, 520). (See also the interesting production of, and awakening from, sleep in dogs by injection of calcium or potassium into the third ventricle, 143, 504, 56. On threshold changes produced by these ions, see 80, 375, 777). Further, ion movements and concentration at membranes have certainly an important rôle in activity and potential maintenance. Local application of an excess of potassium ion, for example, greatly lowers the resting potential of a limited region (486, 100, 362, 300), associated with greater permeability and eventual block; calcium acts inversely (359, 491, 362). (See also 473.) In actual propagation, ion movements under the influence of action potentials have long been invoked; and the suggestion has often been made that potassium ion, because of its greater motility, is carried in excess relative to calcium ion against the polarized membrane and is the direct agent in initiating the colloidal and chemical changes of activity (see Lasareff, 439, 440, 441; also Bethe on hydrogen and hydroxyl ions, 66). Obviously, in interpreting central nervous behavior on such a basis, further postulates

TABLE 5

	MEDULLATED NERVE		NON-MEDULLATED NERVE	CENTRAL NERVOUS SYSTEM	MUSCLE
	Rest	Activity			
Metabolic rate	1	1.3–4.0	10	20+	1
Substance oxidized	Sugar (fat) (protein)	No sugar	Sugar	Sugar	Sugar (fat) (protein)
R.Q.	0.8	1.0		1.0	1.0 or less
Anaerobic CO_2 production	+	−			?
Anaerobic lactic acid production	+	−	+	+	+
Aerobic lactic acid:					
1. Oxidation	−	−	−?	+	+
2. Resynthesis	−	−		−	+
Glycolysis via hexose-phosphate				− (some +)	+
Ratio initial to delayed heat on activity		1:9	1:50		1:1.5
Influence of anoxia on delayed heat		Falls as does initial			Largely disappears at once
Methylene blue effect on respiration:					
1. Normal	Increases	None	Increases		Increases
2. After carbon monoxide inhibition	Very slight restoration				Full restoration
K effect on respiration	Depresses			Stimulates (?)	Stimulates
Ca effect on respiration	Depresses			Depresses	Depresses
Na effect on respiration	None				Stimulates

would have to be added—as regards the time factor, the liberation of ions from or binding in other combinations, and the like. The quantity of inorganic phosphate present at any moment, for example, must affect the available free calcium ion, and this in turn depends on other factors, such as stimulation. Likewise, calcium, magnesium and phosphate, especially, are crucial to several basic enzyme reactions. Certainly the relations between ion effects, membrane state, metabolic events, and conduction in nerve and the central nervous system merit the finest scrutiny.

F. *Central Nervous System. Drug Action.* The actions of a variety of substances and agents on the behavior of nerve, though depending on chemical changes in the tissue, must be omitted from this review; but some of the more important or representative studies of these are included in the bibliography (618, 89, 291, 662, 3, 415, 599, 28, 69, 619, 647, 299, 623). Similarly, the more extensive literature dealing with the chemistry and metabolic activity of the central nervous system must be passed by, though in so doing an important part of each neurone is left in neglect. Recent work has tended to emphasize the iron (and copper) content of the brain (678, 569, 788, 499, 679, 720, 552, 721, 224, 573, 339, 132), the carbohydrate (468, 425, 29, 355, 383, 384, 426, 489, 691, 248, 366, 404, 431, 506, 508, 644, 645, 507, 547, 562, 646, 354, 560, 212, 30, 556, 276) and lipin metabolism (517, 757, 768, 778, 33, 70, 402, 577, 582, 604, 605, 581, 758), respiration (649, 355, 191, 443, 247) and the chemical differentiation of brain regions already distinguished functionally and histologically (292, 293, 716, 792, 246). Work on nitrogen bodies has also progressed (293, 465, 583, 608, 546, 632, 792). Some comparisons between myelinated nerve, non-medullated nerve, central nervous system and muscle, at rest and during activity, are given in table 5. This field, however, is barely scratched; and rich awards of knowledge, from which must arise a fuller understanding of the normal mechanisms of neural activity as well as of their disturbances in human pathology, surely await the investigator who ploughs more deeply into it.

SUMMARY

Recent methodological advances have permitted the certain demonstration in nerve of respiration, heat liberation and metabolic changes during rest and, separately, during activity. The isolated nerve remains essentially normal for a time permitting sufficient study, when kept in an appropriate medium with an adequate oxygen concentration. Non-

neural elements, especially the perineurium, may contribute to the resting metabolism and also confuse experiments by interfering with the free passage of substances or currents. For amphibian nerves, especially, the state of the animal—season, temperature and the like—markedly influences the metabolic condition. Quantitative data on the chemical composition of nerves are summarized.

At rest, frog nerve respires at the same rate as frog muscle, liberating heat equivalent to the oxygen consumed and burning carbohydrate in part. Evidence of the breakdown of phospholipins and possibly proteins exists, but is not conclusive. The respiratory quotient is probably in the region of 0.8.

When the normal oxidations are prevented by oxygen lack or respiratory poisons, the familiar glycolysis appears. Lactic acid once formed, however, cannot be rebuilt into carbohydrate nor even burned when oxygen is again available, which indicates that this substance does not constitute a normal intermediate in sugar oxidation. Absence of lactic acid accumulation under aerobic conditions is rather due to its non-formation than to a continued removal, and oxidation of non-carbohydrate suffices to restrain production. Phosphocreatin is broken down reversibly by any form of interference with respiration.

A nerve does not lose its ability to function for some hours after respiration is stopped, even when glycolysis is also suspended. This is due in part to the existence in nerve of an oxidizing reserve. Possibly substances entering into the chain of reactions of cell oxidations and normally at an equilibrium of partial oxidation become completely reduced and so continue the oxidation of substrate and the production of carbon dioxide. Much evidence indicates that the respiratory catalysts and intermediates in nerve are similar to those found in muscle and other cells. This is derived especially from studies with respiratory poisons, such as cyanide and carbon monoxide, and respiratory accelerators, such as methylene blue.

The resting metabolism of nerve appears to be significant primarily in terms of energy liberation. This normally is obtained from the reduction of molecular oxygen, but to the extent that another oxidizing agent yields sufficient energy on reduction, there is the possibility of maintaining nerve in a functional state with this substance in the absence of oxygen. The energy is utilized primarily in maintaining the cell machinery, such as the state of polarization of partly permeable membranes, involved in survival and activity. Nerve fibre degeneration following section, avitaminosis, and certain forms of toxic neuritis, may

result from lack of a continued supply of oxidation catalysts and consequent lack of the needed energy.

During activity, the total heat liberation, respiration, and chemical processes are increased over their resting values, and different intermediate reactions enter the balance. The quantitative agreement shows that all heat results finally from oxidations. In contrast to muscle, which increases its resting metabolism several thousand-fold during maximal activity, the resting rates are hardly doubled in nerve. The excess activity is not limited to the brief period of conduction and return from the refractory state, but a prolonged and separate recovery phase continues for many minutes more. These late reactions are further evidenced by incomplete recovery of function for a similar time. A given tetanization evokes less metabolic response from a nerve within ten minutes of a previous period of activity than after this time; and the metabolism per impulse falls as successive ones are crowded closer together. Such equilibration changes during activity affect many of the properties of nerve. Although it has been suggested that the respiratory response to electrical stimulation is an excitation effect, it seems to be a true index of conduction. Metabolic, as other active responses of nerve, are independent of the intensity of the evoking stimulus and its quality as natural or artificial.

The carbohydrate changes of rest are not altered during activity, so that sugars do not supply the energy for conduction. The possible participation of galactose from cerebrosides, or of partial oxidation products of the usual carbohydrates has not been excluded. An increased ammonia formation and decrease of combined phosphates also attend activity, probably related in large part to adenylpyrophosphate breakdown. Pnosphocreatin is hydrolyzed reversibly during tetanization and may function in nerve analogously to muscle.

When oxidations are suspended, the nerve does not utilize glycolysis as an energy source for conduction, though by supplying some energy for maintenance this reaction may prolong the time for asphyxial block. Conduction is finally lost when the supply of available energy becomes insufficient, due to exhaustion of an oxidizing or an energy reserve or to changes in state (especially salt distribution) which prevent its utilization. The partial recovery of an asphyxiated nerve in oxygen-free saline does not depend on the out-diffusion of metabolites but on an ion effect. Recovery has also been obtained with m-dinitrobenzene in place of oxygen.

The events associated with activity occur in three phases: conduction,

refractory period and late recovery. It is probable that the reactions of the first are to an extent reversed by energy from the second, which in turn depends on the third. It is possible to relate the heat production, action potentials and membrane changes of activity and recovery to specific chemical reactions, though such a synthesis must long remain tentative.

The pseudo-inhibition of peripheral nerve depends upon excitations that meet interference, but inhibitory stimulation of ganglia may be associated with an actually decreased respiration. This indicates, as does a consideration of several established neuro-humoral reactions at effector organs, that a special production of chemicals or concentration of ions may be involved in the normal transference of activity between a nerve fibre and dendrite or end organ, as well as along the simple axone.

The general problem of metabolism of the central nervous system could not be included, but some of the more important data are given for comparison with peripheral nerve.

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PATHOLOGICAL CALCIFICATION

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Since it is believed that calcium salts are deposited normally only in the formation of bone, pathological calcification, by definition, includes all lime deposits in the soft tissues as well as concretions of calcium salts in the secretory and excretory passages of the body. The subject has excited much attention. Among many excellent discussions, special mention may be made of those by Cohnheim (23), Askanazy (4) and Hofmeister (63) in the older literature, of Wells' masterly Harvey Lecture (166), and of the more recent comprehensive review by Schmidt (132). During the last few years our knowledge of pathological calcification has been greatly extended by studies of calcium deposit in normal ossification and in rickets, and by physicochemical investigations of the state of calcium in the tissues and body fluids. Of special interest is the relationship of calcification to disturbances in parathyroid function and to overdosage with irradiated ergosterol. In the following review an attempt will be made to present the main facts concerning the clinical and experimental incidence of pathological calcification, and to discuss our present knowledge of its pathogenesis and chemistry.

MANIFESTATIONS OF PATHOLOGICAL CALCIFICATION. For purposes of discussion the actual manifestations of pathological calcification may be divided into *a*, dystrophic calcification; *b*, calcinosis; *c*, metastatic calcification; *d*, arterial calcification; *e*, nephrolithiasis. These divisions, while based in part upon real differences in pathogenesis, cannot be sharply delimited and are employed chiefly for convenience in presentation. They are also not inclusive. The discussion of concretions in the salivary, biliary and pancreatic ducts will be entirely omitted. The formation of stones in the bronchi and lungs will not be considered. Heterotopic ossification, or the formation of bone in soft tissues, although properly regarded as a form of pathological calcification, will not be included because the factors involved seem to be essentially those concerned in normal skeletal bone formation.

Dystrophic calcification is the term applied to lime deposits in dead

or dying tissue. Since any area of devitalized tissue which is not absorbed may become infiltrated with calcium salts, the locations and distribution of this form are extremely varied. Dystrophic calcification is found in tissues completely dead, such as infarcts, areas of necrosis and inspissated collections of pus. It occurs in scar tissue which has undergone hyaline changes and may be seen in elastic tissue, as in the internal elastic layer of the arteries, without demonstrable nutritional disturbance. The tissues involved are of widely different origin and chemical character and seem to have in common only the quality of homogeneity and a physical appearance frequently resembling the hyaline cartilage in which new bones are formed. While fibrous and elastic tissues are most often involved, dystrophic calcification may also occur in degenerated ganglion cells of the brain (167), in epithelioma of the skin (115), and in epithelial cells of the kidney when damaged by temporary interruption of circulation (98) or by poisons such as mercury, iodine and iodoform (87). It occurs in areas of fatty degeneration, most strikingly in pancreatic necrosis, but also in malnourished lipomata, in caseating tubercles and in the intimal patches of atheromatous vessels—lesions in which fat frequently undergoes degenerative changes.

The sites of dystrophic calcification are too numerous to mention and the condition is so common that reference to individual descriptions or examples has little significance. Frequent locations are tuberculous lymph nodes, uterine fibroids, thyroid adenomata, healed abscesses and infected serous cavities. Especially remarkable is the calcification of the retained fetus, lithopedion, in which extensive calcium deposit is apparent in soft tissues as well as in the skeleton (6).

All available evidence seems to indicate that dystrophic calcification is dependent upon local conditions and that it is not initiated, although it may be modified (108) (147), by general changes in calcium metabolism or in the state or amount of calcium in the circulating blood.

Calcinosis is the term used to describe a deposit of calcium in or under the skin. It has also been applied to more scattered deposits in the subcutaneous tissues. Cases in the literature have been divided into two groups. *a.* Calcinosis circumscripta is a condition in which calcification is localized to the skin. It occurs almost always in the upper extremities, especially in the fingers, and interferes little with the general health of the patient. This form has frequently been called "calcium gout," although proof has not been offered that there is any close similarity between it and the better known uric acid gout, or that it is

dependent upon any underlying metabolic disturbance. *b.* The designation of calcinosis universalis has been reserved for those cases which reveal, in addition to skin manifestations, a more or less extensive involvement of interstitial tissues, including tendons, fascia, muscles and nerves. The condition is less common than calcinosis circumscripta, affects younger individuals and causes serious, and usually rapid, deterioration of health.

The entire subject has been recently and most completely reviewed by Steinitz (150), who was able to collect from the literature seventy-one cases which he classified as localized, and thirty-four as belonging to the generalized form.

Careful history in circumscribed calcinosis usually reveals that the patients have suffered from cold hands since early childhood, and that the calcium deposits have occurred gradually. The association with scleroderma, which was noted in the case reported by Weber (163) in 1878, has been found in more than one-third of the cases in the literature. In many other cases which cannot be definitely classed as scleroderma the hands have been cold and blue, the descriptions ranging from discoloration and acrocyanosis to a complete picture of Raynaud's syndrome in the patients reported by Logan (101), Brauer (15), and Lewy (97). The relationship of calcinosis to scleroderma and to Raynaud's disease has been thoroughly discussed by Durham (33).

Blood calcium determinations were found by Steinitz in 16 cases, only 4 of which presented unusual features. In Durham's case a serum calcium of only 7.4 mgm. was possibly attributable to concomitant severe nephritis. Mosbacher's (111) record of a serum calcium of 28.0 mgm. in a normal individual is sufficient to invalidate the high values which he reported in calcinosis. Akobdszanjanz (1) found only 12.2 mgm. at first examination in his case, but during menstruation is said to have shown 22.9, a value so high as to cast more than a little doubt upon the accuracy of the determinations. Although Staub (149) found serum calcium of 16 and 17 mgm., the studies in general lend little support to the idea that calcium deposit is dependent upon high calcium values in the serum. Thannhauser (154), in a recent discussion, discards the idea of a generalized disturbance of calcium metabolism and considers the calcification as an expression of locally damaged tissue. Indeed, the frequently observed circulatory disturbance in hands and feet, the known nutritional defect and ultimate gangrene occurring so frequently in scleroderma and Raynaud's disease, make it seem not unlikely that circumscribed calcinosis should be classed as a form of

dystrophic calcification. Pathological observations, however, have been too limited to establish a definite association, and careful studies of the calcium metabolism in calcinosis circumscripta are needed before the possibility of a metabolic disturbance can be abandoned.

Many cases diagnosed as calcinosis universalis have been so classified because of the wide distribution of the lesions and the great severity of the general symptoms. Otherwise, they have differed in no essential respect from cases of the circumscribed form. Eight of the patients regarded by Steinitz as examples of calcinosis universalis had associated scleroderma. Langmead (95), reviewing cases of scleroderma and myositis fibrosa, believed that they were clinical manifestations of a single condition, that both might occur in the same individual and that calcinosis might be found with either or both conditions. Evidence now available is probably insufficient to prove or disprove Langmead's contention. Review of the cases, however, reveals that some of the most severe examples of calcinosis universalis have been unaccompanied by obvious signs of scleroderma or by the actual demonstration of fibrotic lesions in the muscles.

Opportunities of studying the pathological condition in early lesions of calcinosis universalis have been extremely limited, but the available information offers no evidence either of fibrotic or of necrotic changes preceding the deposit of calcium. Versé (158) found the first stage of the process consisted of a colloid swelling of the connective tissue followed by the deposit of extremely fine granules of calcium in the connective tissue fibrils and the elastic fibers. The histological studies of Bauer, Marble and Bennett (10) showed no evidence of preliminary tissue necrosis, the earliest lesion in their case occurring about the periphery of intact fat cells.

Friedländer (39) determined balances of nitrogen, sodium, potassium, calcium, magnesium and phosphorus in a case of calcinosis universalis, but was unable to demonstrate any disturbance of calcium metabolism. More recently, extensive metabolic studies have been reported by Bauer, Marble and Bennett (10), who demonstrated in their case an extraordinary ability of the body to hold absorbed calcium and phosphorus, the tendency being greater for calcium. Fecal and urinary values of calcium excretion were low and remained so regardless of food or medication. The authors concluded that these determinations indicated an abnormal affinity of the tissues for calcium, a property possibly limited to soft tissues since the x-rays failed to demonstrate excessive calcium retention in the bones. Neither Friedländer nor Bauer, Marble and

Bennett could demonstrate any abnormality in the serum calcium and phosphate. From the literature, Steinitz collected serological studies of seven other cases, none of which revealed significant deviations from normal. Tisdall and Erb (155) also found normal values which they thought argued against a metabolic disorder. The studies of Bauer, Marble and Bennett, however, indicate the possibility of a definite disturbance in calcium metabolism not mirrored in the values for serum calcium. It seems most important that the studies of Bauer and his associates should be extended to cases of calcinosis circumscripta as well as to other cases of calcinosis universalis.

Metastatic calcification. The original description of metastatic calcification by Virchow (159) in 1855 was based on observation of five cases of destructive disease of bone associated with more or less severe nephritis and of one case in which nephritis was unaccompanied by any demonstrable changes in the skeleton. From this study, Virchow proposed that destructive bone lesions could cause an excess of calcium salts in the blood stream, which, if not promptly excreted by the kidneys, might be deposited in soft tissues where there had been no previous tissue damage.

In human pathology the condition is extremely rare. Askanazy (4) in 1901 found only 21 cases. Hofmeister (63) added 2, together with one in a dog and another in a rabbit. Wells in 1915 knew of 32, including his own. In the literature published since his report we have encountered records of only 10 cases (62) (30) (70) (119) (136) (8) (40) (104) (107) (12).

In this form of calcium deposit there is no evidence that the organs involved have been the site of any previous destructive change. The lesions have been located chiefly in the kidneys, in the gastric mucoca and in the lungs. The kidney infiltration has consisted of an incrustation of connective tissue stroma with no special localization in the cortex or medulla, the involvement being both in the epithelium and the lumen of tubules. In the gastric mucosa the deposits have been limited to the interglandular tissue about the open end of the glands of the fundus, in a portion corresponding to the location of the acid secreting cells. The pulmonary involvement consists of an infitration in the connective and elastic tissue of the alveolar walls, in the capillary walls and occasionally in the elastic fibers of small arteries and veins. Not infrequently there is calcification of the pulmonary veins and of the wall of the left auricle. Much more rarely there is involvement of peripheral arteries. Such unusual locations as the back of the trachea (136), the

arteries of the skin (98), and the liver (104) may be mentioned. In the case of Dawson and Struthers fine granules of calcium salts were distributed in practically every organ and tissue of the body. The amount of the deposit is indicated by the study of Tschistowitsch and Kolessnidoff (156), who found that 13.39 per cent of the dried weight of the lung and 12.15 per cent of the dried kidney was composed of calcium oxide.

Metastatic calcification is usually seen as a feature of destructive bone lesions. Its incidence in multiple myeloma has recently been studied by Wallgren (161). Versé (157) and Wells (168) observed it in myelogenous leukemia. Extensive deposits have been found in association with sarcoma (159) (98) (96) (148) (4) and with carcinoma (157) (55) (84) (53) metastatic to bone. Schulze (136) reported such calcification in a case of Albers-Schönberg disease. Its association with osteomyelitis and with caries of the spine was noted by Virchow (159) and has been recorded by several others, including Czech (28), Jadassohn (73), Babes (5), Schulze (137), Küttner (92), and Roth (128). Finally it has been observed several times in cases of hyperparathyroidism in which parathyroid tumors and ostitis fibrosa cystica have been associated. Cases in the older literature were reviewed by Barr and Bulger (8). The recent case of Berner (12) should be mentioned.

The undoubted relationship of nephritis to metastatic calcification has excited much interest. The cases of Kischensky (75), Stade (148), Chiari (20), Hlava (61), Kockel (85), Schmidt (131) and McCordock (107) may be mentioned as examples of calcium deposit in which no important concomitant factor other than severe nephritis was apparent. Marsden (104) found widespread calcium metastases in an infant whose renal disease was accompanied by septicemia. To Virchow and to many later observers nephritis seemed a necessary second factor for the production of calcium deposits in skeletal disease, and it is indeed difficult to find cases in which a renal element can be definitely excluded. Kockel (85) states that there was no nephritis in his case of carcinomatous destruction of vertebrae. The interesting case of Dawson and Struthers (30) may be mentioned as another possible exception.

Calcium metastases, so rare in human pathology, may be produced experimentally by several procedures. Calcium deposits distant from the site of injection were reported by Tanaka (151) and Katase (75) following intravenous and intraperitoneal injections of calcium salts. Although these experiments indicated the possibility that calcium deposits might occur in previously healthy tissue, the calcifications

distant from the site of injection were not of the classical location for calcium metastases and were not obtained at all in the observations of Staub (149). Typical metastatic calcification was produced, however, by Rabl (124) in experiments in which he alternately added acid and alkali to a high calcium diet. This work was confirmed by Dreyfuss (32) and by Kleinmann (78), who found, however, that they could induce calcium deposit by addition of acid alone.

The method most frequently employed to produce metastatic calcification experimentally has been the administration of parathormone (71) or of toxic doses of irradiated ergosterol (91) (146) (57) (145) (93). The calcium deposit is found in the lungs, gastric mucosa, kidneys and arteries, and corresponds in every essential particular with clinical calcium metastases. In these experimental procedures evidence of local tissue damage preceding the deposit has seldom been disclosed (93).

Metabolic conditions accompanying the metastatic calcification of Rabl's acid and alkaline diets have not been completely studied. Kleinmann (81) found that acid feeding increased the excretion of calcium and phosphorus in animals while an alkaline diet lessened it. Changes accompanying parathormone administration have been carefully determined. According to Albright and his associates (2) small doses produced first an increase in phosphorus excretion followed by a fall in phosphorus and a reciprocal rise of calcium in the serum. Toxic doses on the other hand, as Collip (25) found, cause elevation of calcium with great increase of calcium in the urine and later an elevation in serum phosphate. The metabolic changes resulting from viosterol have been recently examined by Bauer, Marble and Claflin (11). Small or moderate doses produce no constant changes. Somewhat larger amounts altered the relationships of urinary and fecal excretion, with minimal changes in the balance and in the serum values of calcium and phosphorus. Toxic doses, on the other hand, have produced changes which are not distinguishable from large amounts of parathormone (53) (77).

Although the effects of the two substances are so nearly identical, their relationship to each other has not been clearly established. Several observers have found that vitamin D raises serum calcium in parathyroidectomized dogs, and have inferred that the vitamin has an effect on the level of serum calcium independent of the parathyroid hormone. This belief is based on the probably unsafe assumption that parathyroid tissue can be completely removed. Taylor, Branion and Kay (152) show that in animals from which the parathyroid glands were removed by the usual routine operation the resulting hypocalcemia

could be corrected by doses of potent irradiated ergosterol. In a second group of animals, in which the parathyroid tissue was removed by exceedingly careful technique, the effect of the same dose in the control of tetany was greatly reduced, and the animals of the group could not long be kept alive. In a third group, a large dose of irradiated ergosterol caused death with symptoms characteristic of hyperparathyroidism. These experiments as well as the almost complete similarity between the physiological actions of parathormone and toxic doses of irradiated ergosterol suggest that the vitamin accomplishes its injurious effects, including the calcium metastases, through a stimulation of the parathyroid glands.

Arterial calcification. The relationship of general and local factors in the development of arterial calcification has attracted much attention. Two main types of arteriosclerosis are usually considered. In atherosclerosis the changes appear primarily in the intima and include fatty infiltration, hyalinization and necrosis of intimal cells. The deposit of calcium occurs at first in small granules which later may become conglomerate. The media may show surprisingly few changes. Medial calcification is often called Mönckeberg's sclerosis, although it had been noted by others before Mönckeberg's (109) excellent description. In this type changes occur primarily in the media and consist of degeneration in smooth muscle cells and elastic elements. Fatty infiltration and hyalinization may also be seen. Calcium salts are deposited as extremely fine granules in hyalinized interstitial tissue, the amount gradually increasing to form trabeculae. There may be almost complete involvement of the medial layer without evidence of intimal change.

It is thus seen that both types, atherosclerosis as well as medial calcification, depend on factors, such as fat infiltration, degeneration, hyalinization and necrosis, which ordinarily precede dystrophic calcification. Unusual deposits of calcium in arteries have been observed, however, in conditions in which there is a general disturbance in calcium metabolism. The experiments of Rabl (123) already quoted induced calcium infiltration in all arterial coats as well as in the lumina of arteries. Hueper (71), by administration of parathormone, showed calcification of the walls of renal arteries, together with a widely disseminated calcification of tissues. Much more striking changes in arteries were shown by many observers following the injection of irradiated ergosterol. Kreitmair and Moll (91) demonstrated a deposit of calcium both in and on the vessel walls. Large blood vessels as well

as small were transformed into stiff tubes. These changes were studied in a more detailed manner by Kreitmair and Hintzelmann (90) and by Wenzel (171), and have been substantiated by many others (53) (57) (93). Smith and Elvove (146) were able to demonstrate by chemical analysis an enormous increase in the calcium content of the aorta.

In human pathology, calcification of blood vessels associated with defects in calcium metabolism has been rarely encountered. In the leukemic cases of Verse (157) and Wells (168) the pulmonary veins and the left auricular wall were extraordinarily involved. Similar changes were apparent in the cases of Schulze (136) and of Jadassohn (73). Davidsohn (29), and later Lazarus and Davidsohn (96), found localized calcification in the wall of the left auricle.

In a few cases in the literature, calcification of peripheral arteries has been unaccompanied by deposit in other locations. Küttner (92) observed a boy with purulent destruction of the bones of the back, with visibly increasing arterial calcification and extensive medial calcification of peripheral arteries. Schulze (137), Müller (112), and Barr and Charles (9) showed calcium deposits in peripheral vessels with severe generalized osteomyelitis. The combination of typical calcium metastases in lungs, stomach and kidneys with disseminated calcification of the arterial system was seen by Schulze (136) in osteosclerosis and by Schmidt (131) in a case of nephritis. It was also observed in three patients with parathyroid tumors and ostitis fibrosa cystica (30) (70) (37).

An extraordinary, localized calcification of arteries was described by Magnus Levy (103) in a woman of 47 with cardiac decompensation. The involvement was demonstrated by x-ray and was shown to be localized to the larger arteries and extremities and over a limited portion of their source in the cubital and popliteal regions. There was also a calcified nodule in one forefinger. This case was observed by Cohn and Salinger (22) thirteen years later, when the calcium deposits had assumed enormous proportions. Steinitz (150) may be correct when he includes this case in the category of calcinosis. It is interesting that the cases of Verse (158), Fontana (37) and Durham (33) revealed, in addition to calcinosis, a considerable calcification of blood vessels.

The nature of the supposed calcification of arteries in ostitis deformans, Paget's disease, is not well understood, although the association has been emphasized by many writers. The tortuosity of the temporal vessels has been pictured by Pescorola and Bertolotti (120), and by Ely (34). Calcification of the media of suprarenal vessels with extreme

arteriosclerosis was seen in an old man described by Cone (26). Higbee and Ellis (60) showed calcification of the media in thyroid and pancreatic vessels. Although premature calcification of arteries in Paget's disease is usually assumed (99), it has excited little special study, and since ostitis deformans is generally a disease of later life, there must be a question as to how much of the changes in vessels can be attributed to disturbed calcium metabolism and how much to variations consequent on the degenerative processes of old age.

Of considerable interest is the localization of arterial calcification in these cases which are not dependent upon local causes. Generally the intima is not involved and the process seems to have no relation to the usual forms of atherosclerosis. In some experimental animals and in Dawson and Struthers' (30) case all coats were involved. The site of election seemed to be the media in Schulze's (136) case of osteosclerosis. In Küttner's (92) case the intima was incrusted with little actual infiltration of the vessel wall. Barr and Charles (9) found calcification of the media in the vessels of the internal organs but a localization in the internal elastic layer in the peripheral arteries. Observations with Policard's ashing method indicate that there is no strict localization, that calcium content is increased throughout the vessel, and that ordinary staining methods for calcium merely emphasize the more obvious sites.

Urolithiasis. Phosphatic calculi composed both of calcium and magnesium phosphate are the stones usually found in derangements of calcium metabolism. It must be remembered, however, that urinary calculi are seldom pure and that stones predominantly composed of urates or oxalates may have layers of calcium and magnesium phosphates. Under such circumstances it is quite impossible to judge how much importance changed excretion of calcium salts might assume in the formation of a large variety of stones. Although the pathogenesis of urolithiasis is by no means clear, clinical as well as experimental evidence seems to indicate that infection, stasis in the urinary tract, and desquamation of the lining cells of the pelvis are factors of great importance, factors which are obviously beyond the scope of this review. We may, however, inquire briefly to what extent general disturbances in calcium metabolism can contribute to calculus formation. Urolithiasis has not been found following the injection of large amounts of lime salts (151) (75). Hueper (71) found calcium casts but no calculi in his dog following injection of parathormone. Similar changes were shown by Smith and Elvove (146) with the metastatic calcification following

viosterol intoxication. Neither in these nor in the majority of experimental studies of viosterol administration have kidney stones been seen. Dixon and Hoyle (31), however, observed renal and bladder stones in rats fed with large doses of irradiated ergosterol. This work was confirmed by Hoyle (69).

Urolithiasis has been found with a great number of bone diseases. Possibly the most common association is with injuries to the vertebrae. This has been emphasized by many authors, including Müller (113), Kocher (86), Holländer (64), Simon (144), and Seefisch (138). The literature has been reviewed by Wagner (160). Such accidents have been accompanied by injuries to the spinal cord, extensive paralyses, loss of bladder control, frequent catheterization, cystitis, and ascending urinary infection. Thus the destruction of bone and its subsequent repair with resorption and deposit of calcium salts are combined with many other factors. The association of stones with other simple fractures has been less frequent. Cabot (18) observed it in association with a crushing injury of the femur. Stones followed an uncomplicated fracture of the tibia in a case reported by Weber (164). Noland and Conwell (116) have reported the association with fracture of the pelvis.

There is an apparent relationship between infected compound fractures, osteomyelitis and tuberculosis of the bone. The work of Mayet, (106), Paul (118), Weber (164), and Borman (14) may be mentioned. Immobilization and muscular inactivity have also been considered as important factors both in the atrophy of bone and in the formation of kidney stones. The studies of Hoppe-Seyler (67) and of von Noorden (117), although incomplete, indicated an increased calcium excretion in immobilized patients.

In all of the circumstances which have been cited, factors other than the bone changes may have been important in the formation of kidney stones. For this reason the recently observed relationship between hyperparathyroidism, ostitis fibrosa and kidney stones is of great importance. In Hunter's (72) 32 cases of proven hyperparathyroidism and ostitis fibrosa, 10 had renal calculi. It has not been shown that ostitis fibrosa has any characteristics of an infection or that it is complicated by stasis or primary disease of the urinary tract.

From this evidence it seems quite probable that kidney stones may be associated with general changes in calcium metabolism, and under special but not well understood conditions may develop in cases subject to metastatic calcification and characterized by hypercalcemia.

FACTORS INFLUENCING THE DEPOSIT OF CALCIUM SALTS. The various

observations upon the incidence and form of calcium deposits have led to a great number of more or less well conceived theories which are not only quite dissimilar in their fundamentals but are not entirely comparable since some have dealt only with dystrophic calcification while others are concerned with the explanation of metastatic calcification and the similar deposits which have been experimentally produced. Calcium salts in the tissues must be derived from the blood serum and other body fluids. Removal and precipitation might be accomplished by changes in the solubility of inorganic ions in the tissue fluids and tissues, or they might be attributed to chemical substances in the tissues possessing a special affinity for calcium. While at the present time no all embracing explanation for the phenomena of calcification can be offered, the importance of the various factors may be examined.

State of calcium in blood and tissue fluids. The conditions under which calcium exists in the body fluids have been thoroughly discussed by Klinke (82) and have been recently and critically reviewed by Peters and Van Slyke (122). Under physiological conditions the calcium concentration of serum is almost constant, varying in humans only between 9.0 and 11.5 mgm. per 100 cc. It is not easy to raise the serum concentration of calcium by ingestion or injection of calcium salts in large amounts. Even intravenous and subcutaneous administration causes only a transitory rise (21) (74), although by continuous intravenous injection Collip (24) was able to maintain a high level in the serum.

Injection of sufficient amounts of parathyroid hormone, however, produces hypercalcemia (25) without extra intake, or indeed without any intake of calcium salts (58), and in spite of the increased excretion incident to the injection (50). Parathyroidectomy, on the other hand, may produce a fall to a value less than one half that found in normal serum (129). Although administration of large amounts of calcium salts tends to restore calcium values to their normal level (102), the treatment must be constantly repeated if normal values are to be maintained. In view of these observations, it is interesting that Hastings, Murray and Sendroy (55) could influence the solubility of calcium in salt solution by the addition of parathormone, although it is somewhat puzzling that the serum of parathyroidectomized animals can dissolve as much calcium as normal. Greenwald (48) suggested that parathyroid hormone is necessary for the preparation of an organic compound of calcium, which seems to have some resemblance to calcium citrate, and which is most important in keeping calcium values of tissue fluids at their physiological level. Klinke (83) has recently offered evidence of

the existence of an unknown calcium compound in blood by demonstration that in an ultrafiltrate of serum exposed to an electrical field calcium wanders not only to the cathode but also to the anode.

However it may be accomplished, there can be little doubt that parathormone increases the amount of calcium salts which may be held in solution by tissue fluids. The extremely low values for serum calcium obtained in parathyroidectomized animals indicate that a large portion, possibly 40 or 50 per cent of the normal calcium content of serum, is kept in solution by this mechanism. The occurrence of tetany on the one hand and of hypercalcemic symptoms on the other shows that this fraction in whatever form it may exist is physiologically active.

Another large part of the calcium content of serum, as well as some other body fluids, appears to be unaffected by parathormone (3) (130) and depends upon the protein content. Spinal fluid and protein free edema fluid have only about 5.0 mgm. of calcium per 100 cc. (51) (52), while joint fluids, which contain amounts of protein almost as great as serum, were shown by Cajori, Crouter and Pemberton (19) to hold as a much as 10.7 mgm. of calcium per 100 cc. The relationship of calcium solubility to protein is indicated also by in vitro experiments. Greenberg and Schmidt (47) showed that at the pH of the body, calcium is bound to casein in a complex non-ionized form. Loeb and Nichols (100) found that in solutions of euglobulin and pseudoglobulin the diffusibility of calcium diminished as protein content increased. By comparison of the calcium concentrations in sera and transudates containing varying concentrations of protein, Hastings, Murray and Sendroy (55), and Peters and Eiserson (121) estimated the amount of calcium bound to protein. Calculating with their formula, in a serum of normal reaction containing 7 per cent of protein, approximately 4.0 mgm. would be held in solution by protein. The physiological activity of the fraction of calcium bound to protein has not been demonstrated. Clinical conditions such as nephrosis may be accompanied by low calcium values without tetany or abnormal excitability.

If approximately 40 to 50 per cent of the total serum calcium is dependent upon the presence of parathormone, and 3 to 4 mgm. are held in solution by protein, there remains only a small amount to be accounted for by the forces which ordinarily govern solubility in salt solution.

The attempt of Neuhausen and Marshall (114) to determine calcium ion concentration directly by means of the calcium amalgam electrode indicated values of 20 +5 per cent of the total serum calcium. Because

of difficulties in the method this yielded no conclusive results. It is interesting, however, that Corten (27), using a new and improved electrometric method, found calcium ion concentrations approximating 2.0 mgm. with variations of about 20 per cent. Brinckmann and van Dam's (16) estimation of calcium ions by utilizing the solubility product of calcium oxalate has been much criticized both because of doubt concerning the true value of the solubility product (135) (110) and because of its failure to account for activity coefficients (162). Calculation of the amount of calcium salts dissolved in serum by the ordinary forces of solubility was made by Holt, LaMer and Chown (65), in bicarbonate solutions by Warburg (162), and by Hastings, Murray and Sendroy (55), and in solutions containing both $CaCO_3$ and $Ca_3(PO_4)_2$ by Sendroy and Hastings (140). It may be said that none of the estimates for calcium in solution due to ordinary solubility forces exceed 25 per cent of the total. The subject presents extraordinary difficulties and all of the factors have not been determined. For a more extended discussion of the main questions involved the reader is referred to Kleinmann (79).

It may be agreed that calcium salts are dissolved in body fluids not only in simple solution, but also in combination with proteins and in an ill defined form which depends upon the presence of the parathyroid hormone. Neither the precise amounts nor the form, degree of ionization or physiological importance of each fraction can be definitely stated. The changes in each fraction induced by variations in the others have been only partially investigated.

Analyses of inorganic substances in tissue fluids indicate that the calcium in simple solution is chiefly in combination with phosphate and carbonate in the form of relatively insoluble salts. The exact compounds formed by calcium with carbonate and phosphate in tissue fluids, although of great importance in the consideration of factors which may lead to precipitation are not definitely known. The usual assumption that they consist of tertiary calcium phosphate and calcium carbonate, while still tenable, has been questioned by Shear and Kramer (141), who show that serum is actually undersaturated for $CaHPO_4$ and suggest that calcium and phosphate ions may be so combined in tissue fluids. While their theory has excited much interest, analytical evidence for the existence of $CaHPO_4$ in serum is completely lacking and analysis by physical methods (153) (127) has failed to demonstrate it either in bone or pathological calcifications.

It has also been suggested by several observers (41) (42) that calcium phosphate and calcium carbonate might be combined in a complex

salt. Again positive analytical evidence of such a combination is almost entirely lacking and Kleinmann's experiments have indicated the complete dialyzability both of carbonate and phosphate ions.

Whatever may be the compounds of calcium with phosphate and carbonate, there is general agreement (65) (55) (122) that the amount of calcium dissolved in serum is greater even after deduction of the protein fraction, than can be held by a salt solution of similar phosphate and carbonate content. This might be attributed to the formation of some unknown compound through the agency of parathormone or to supersaturation of the serum with calcium phosphate, calcium carbonate or both. When serum or spinal fluid is placed in contact with $Ca_3(PO_4)_2$, calcium is removed from the solution. The calculations of Holt, LaMer and Chown (65) seem to offer convincing proof that serum is supersaturated with calcium phosphate, a phenomenon which they explain as due to the extremely slow rate at which the last portions of calcium phosphate precipitate from solution. Sendroy and Hastings (139), however, found that inoculation of serum with $Ca_3(PO_4)_2$ was followed by a fall of carbonate as well as calcium values and that calcium carbonate was precipitated. They also showed that the addition of solid calcium carbonate caused no precipitation. These results offered no evidence of supersaturation with carbonate and were difficult to explain on the basis of supersaturation with phosphate. Kleinmann (79) was able to confirm the work both of Holt and his associates and of Hastings and Sendroy. He found that addition of solid $Ca_3(PO_4)_2$ removed both Ca and CO_3 ions from solution in serum and that no loss occurred from addition of solid $CaCO_3$. From these experiments, he inferred, however, that serum is supersaturated with $Ca_3(PO_4)_2$ and that inoculation with crystals of this salt causes the precipitation of $Ca_3(PO_4)_2$, which is accompanied by a second reaction. Through an exchange absorption a portion of the precipitated phosphate is transformed into $CaCO_3$, a change accomplished by removal of CO_3 ions from the serum and loss of PO_4 ions from the precipitate.

Klinke (83) questions the theory of supersaturation on several grounds and particularly because precipitation of Ca from solution can be caused not only by solid $Ca_3(PO_4)_2$ but also by freshly prepared $BaSO_4$ and Al $(OH)_3$, agents which are known to have an adsorptive influence. He also shows that in the so-called exchange absorption of Kleinmann, the CO_3 and Ca do not disappear from solution in stoichiometric proportions.

Whether or not there is supersaturation of calcium phosphate in serum, the equilibrium of the solution can be easily disturbed and pre-

cipitation may occur under a wide variety of circumstances. Many of the factors which influence the deposit of calcium salts may be examined separately.

Effects of hypercalcemia and hypocalcemia. If serum and other body fluids were only normally saturated with $Ca_3(PO_4)_2$, an increase of calcium ions, if accompanied by no other changes, should lead to the precipitation of $Ca_3(PO_4)_2$. Since hyperparathyroidism and the administration of excessive doses of irradiated ergosterol produce both high values of calcium in the serum and pathological calcification, a predictable relationship between the degree of hypercalcemia and the deposit of calcium in the tissues might be expected. It is difficult to find experimental or clinical conditions in which serum calcium values vary without concomitant changes of possible or recognized importance. Injections of large amounts of calcium in which at least a transitory hypercalcemia is inevitable have induced only patchy calcification (151) (75), or in some instances no changes in parts distant from the site of injection (149). Most extensive destruction of bone, although almost certainly accompanied by temporary increase in serum calcium, leads only occasionally to demonstrable deposits of calcium in soft tissues. Smith and Elvove (146), in their experiments on ergosterol poisoning, were able to compare the chemical analysis of tissue with calcium values in serum. In several observations enormous calcium deposits were found in tissues with only slight increase in serum calcium. On the other hand, some experiments in which serum calcium was raised to approximately 50 per cent above normal revealed no perceptible increase of calcium in any of the tissues examined. They concluded that hypercalcemia of itself is not sufficient to account for abnormal deposits of calcium in tissues. It is even more significant that Shelling (143) found calcification of soft tissues with hypocalcemia. In parathyroidectomized rats which showed defective calcification in the growing zones of bone, he observed extensive calcification of lungs and blood vessels.

Influence of serum phosphate. The lack of parallelism between the level of serum calcium and calcium deposit is not surprising when it is remembered that calcium and phosphate ions, if other conditions remain constant, bear a reciprocal relation to each other. Any considerable increase in the concentration of phosphate may disturb the equilibrium sufficiently to cause the precipitation of calcium salts. Peters and Eiserson (121), from combined data on calcium, phosphates and proteins, have attempted to evaluate the influence of phosphate in the serum. Although their formula is not applicable to all conditions (49), they

have shown clearly that serum calcium cannot be properly interpreted unless both protein and phosphate values are simultaneously determined.

The influence of phosphate on the deposit of calcium in normal growing bone has been extensively studied in rickets. Its influence in pathological calcification has also been indicated by Smith and Elvove (146), who found in their experiments with viosterol poisoning that the relationship of calcification in tissues to phosphate values in sera could be clearly established. High serum phosphate, accompanied by only a slightly increased serum calcium, generally resulted in great calcification of soft tissues. On the other hand, no abnormal deposition of calcium was found in any case in which the serum phosphate values were low, even when these were combined with pronounced hypercalcemia. Shelling (142) found that animals fed with a minimal calcium and a high phosphorus ration were extremely susceptible to viosterol, succumbed quickly to small doses, and exhibited most profound calcification of soft tissues. He showed further that increased phosphorus retention characterized the metastatic calcification observed with hypocalcemia in parathyroidectomized dogs. It is also of interest that in Rabl's experiments phosphates were used both in the alkaline and in the acid diets.

The relation of phosphate level to calcification in clinical conditions has not been completely studied. In Albright's (2) experiments, already quoted, it was shown that in hyperparathyroidism the first change was a fall in phosphate values followed by hypercalcemia, conditions which persist through the greater part of the course of clinical hyperparathyroidism and which are demonstrably favorable to the removal of calcium from bone. It would be surprising if these same changes were responsible for the deposit in soft tissues, more particularly in the light of Smith and Elvove's experiments where hypercalcemia without elevation of phosphate values was insufficient to cause calcium deposit. It does not seem unlikely that the calcium metastases which are first recognizable at autopsy may occur in the later stages of hyperparathyroidism when hypercalcemia or normal serum calcium is accompanied by hyperphosphatemia. The relation of phosphate retention to the calcification occasionally noted in nephritis has not been accurately determined.

Effect of the degree of alkalinity. If all the calcium in the serum were ionized the calcium content of serum at a fixed HCO_3^- concentration would vary directly with H^+ ion concentration. Such parallelism cannot be expected since, as has been shown, the ionized calcium of the serum does not constitute more than 25 per cent of the total. Other

conditions being constant, however, the solubility of calcium salts is diminished and the likelihood of calcium deposit is augmented by increasing alkalinity. This important fact was early utilized by Askanazy (4) and by Hofmeister (63) to explain the classical locations of metastatic calcification as the tissues from which acid had been excreted or secreted and which were therefore more alkaline in their reaction. The calcification of renal tubules, gastric glands and pulmonary alveoli could be readily explained because of the loss of acid from the cells at these sites. Hofmeister (63) suggested that the calcification of arteries might be explained because of the lowered carbon dioxide tension and increased alkalinity in arterial blood. He also advanced the hypothesis that when a tissue becomes saturated with calcium salts any decrease of CO_2 in solution will cause precipitation.

Changes in alkalinity have also been designated as a factor in the association of metastatic calcification and nephritis. Virchow's explanation of the deposit as secondary to insufficient excretion seemed artificial when it was recognized that the greater part of the calcium is excreted by the large intestine. Rabl (124) wished to explain the association on the basis of disturbed acid base equilibrium. He reasoned that in severe nephritis a diminished alkalinity could lead to the solution in the tissue fluids of a greater quantity of calcium salts, which, with an alkaline diet or other factors causing rapid increase in alkalinity, might be precipitated. His experiments with mice, in which high calcium intake was combined with repeated shifts from highly acid to highly alkaline diet were interpreted as supporting this idea. Kleinmann (81), however, questioning Rabl's conclusions, showed that acid and alkaline diets caused great changes in the renal excretion of calcium and phosphate, factors which, as has been seen, might in themselves influence calcium deposit.

Local causes: a. Fatty degeneration. Observation of calcification in areas of pancreatic necrosis led early to the idea that splitting of fat was connected in some way with the deposit of calcium. This conception was strengthened by the observations of Tanaka, working under Hofmeister (63), who thought he was able to show by test tube experiments that fatty tissue in contact with a solution of calcium salts was calcified through the formation of calcium soaps. Klotz (84), although admitting after analyses that fats and fatty acids are not involved in the calcification of normal bones, advanced the hypothesis that calcareous degeneration is preceded or accompanied by deposits of soapy material. He made no chemical analyses but by staining methods

designed to show calcium, fat, fatty acids and soap, believed he could demonstrate that soap exists in areas of chronic inflammation before lime is deposited, that following soap formation calcium salts are immediately attracted from the surrounding fluid and that the soap and fats disappear from the area and are gradually replaced by calcium phosphate and carbonate. He studied calcified areas in arteries, thickened pleura and in the kidney poisoned by mercury, copper and lead, in all of which he showed similar changes and relationships. Aschoff, in elaborating Klotz's theory, thought that the destruction of intimal cells in the aorta is accompanied by the deposit of cholesterin esters which are broken down into cholesterin and fatty acids, the latter of which combine with calcium to form soap.

This theory of calcium deposition has been seriously questioned almost since the day it was advanced (165). Faber (35) was able to show calcification of the media of the aorta as early as the tenth year and of the pelvic arteries at all ages. His work was amplified by Farkas and Fasal (36), who found calcium deposits in all arteries before the age of twenty. Hesse (59) has recently made chemical analysis of aortas and femoral arteries which showed no visible atheromatous changes and has found that there is an increase of the calcium content dependent upon age and apparently not associated with degenerative changes. Thus at the age of one to two years, the average calcium content of a vessel is 0.16, at thirty-four 0.38, and at fifty-six 1.97. Schönheimer (133) (134), analyzing the lipoids in the aorta, found that the percentages of cholesterin esters did not differ in the calcified and uncalcified portion of the aortic wall and also that the composition of calcified plaques in the aorta corresponded almost exactly to that of a rib from the same individual. Baldauf (7) also found that aortic calcification had essentially the same composition as that of bone. Wells (166) found that calcium soaps could not be extracted from tissues undergoing calcification, even in such lesions as tuberculous lymph nodes in which the pathological process might be considered progressive. On the other hand, calcium phosphate and carbonate could be found at any stage in the process. Hofmeister points out that in experiments in which large amounts of calcium are injected, distant calcium deposits may be found within twenty-four hours, an interval presumably too short to provide for the preliminary deposition of fat and the formation of fatty acids. Wells (169), summarizing the evidence in his recent review of the chemistry of arteriosclerosis, considers that no proof has been offered that calcium soaps are or can be transformed in the tissues into calcium

phosphate and carbonate. On the contrary calcium soaps introduced into living tissues are absorbed and removed, and are not transformed into inorganic calcium salts (170).

b. The formation of phosphoric acid in tissues. The announcement of Grandis and Mainini (46) in 1900 that the phosphorus of ossifying cartilage could be converted from organic combinations into an inorganic form which removed calcium from the blood was much questioned, both on the basis of method and of probability. Robison (44) (125) and his associates, however, have recently demonstrated an enzyme in cartilage which acts upon acid soluble organic phosphorus compounds of blood with the release of free phosphoric acid. This phosphatase exerts a similar action on glycerophosphates and on hexose mono- and di-phosphates in vitro. Robison and Soames (126) have secured in vitro calcification in solutions of glycerophosphate. On the basis of these experiments Robison proposes that at sites of ossification the enzyme converts organic acid soluble phosphates to inorganic phosphates with sufficient local increase of phosphate concentration to exceed the solubility product of $Ca \times PO_4$ and to precipitate $Ca_3 (PO_4)_2$. Thus far it has not been shown that there is in devitalized tissues any substance comparable to the phosphatase of Robison, although the possibility that local increases in phosphate concentration in tissues may play an important rôle has by no means been excluded.

c. Protein combinations with calcium. The possibility of protein combinations with calcium in the tissues was studied extensively by Freudenberg and György (38). These investigators tested the calcium content of cartilage under varying degrees of acidity and from their experiments drew the conclusion that calcium phosphate was combined in a complex molecule with protein. They showed that although cartilage could bind more calcium than other tissues, similar combinations might be formed with other proteins such as casein, gelatin and albumen. Explanation of why the tendency to calcification implied by such a property of proteins is not more generally operative was offered in experiments showing that a great number of metabolic products, including amino acids, creatin, urea, and even sugar, could hinder or prevent the combination of calcium with protein. Attempts to apply these test tube experiments to the physiological problems of calcification met with serious difficulty. Analyses of areas of calcification revealed only a small amount of protein and a relatively large amount of calcium. The explanation that protein serves chiefly to fix calcium with prompt subsequent formation of calcium phosphate and calcium carbonate

requires further confirmation. That proteins on the alkaline side of their isoelectric point can bind calcium there can be no doubt, but that this factor plays an important rôle in the local fixation of calcium in tissue is yet to be proven.

d. Alkalinity of dead and dying tissues. A far simpler explanation of the localized deposit in devitalized tissue has been offered by Kleinmann, (81) who measured the alkalinity in dead tissue in comparison with that of undamaged organs. For this purpose he used the kidneys of rabbits which had been necrosed and calcified by ligation. His measurements were made electrometrically on press juices and scrapings made from necrotic and normal tissues. Although he was able to obtain only comparative values, he believed he could show that the organs subject to dystrophic calcification had a more alkaline reaction than fresh tissues prepared in the same way.

Summary of factors influencing calcium deposition. Solid calcium phosphate in serum and spinal fluid will remove calcium and carbonate from solution. Calcium concentration, phosphate concentration and the degree of alkalinity in serum and tissue fluids are of importance in the solubility or precipitation of calcium salts. Local changes of any of these factors in the tissues themselves may, if unaccompanied by other opposing changes, influence calcium deposition, and since no more specific calcium binding substances have been demonstrated, must be regarded as of possible importance in the localization of pathological calcification.

Kleinmann (78) has attempted to show that both metastatic and dystrophic calcification are dependent upon common factors and that all calcium deposition in tissues commences with the formation of crystals of tertiary calcium phosphate. The deposition of these crystals may be induced because of an increased alkalinity or because of an increase in calcium or in phosphate concentration. Local and general conditions may contribute to these changes. Thus in the metastatic calcification accompanying the toxic action of parathormone and vitamine D, hypercalcemia and later hyperphosphatemia may be of importance. The localization of the calcification may be determined by differences in alkalinity in certain tissues, such as lungs, stomach and kidneys. In devitalized tissues, on the other hand, local causes may be in themselves sufficient without changes in the composition of serum or tissue fluid. Kleinmann's demonstration of the alkalinity of such tissues becomes of importance in determining the site of original deposition of crystalline tertiary calcium phosphate. According to this theory

the presence of a solid phase of $Ca_3(PO_4)_2$, however it may have been formed, has the effect in the tissues as in the test tube of drawing calcium and carbonate from solution and of forming a mixed precipitate of calcium phosphate and calcium carbonate.

Kleinmann's theory is attractive in its inclusiveness and its apparent dependence upon well established principles. As has been seen, however, it is based upon the conception of supersaturation which is still subject to question. Quantitative estimation of the CO_3 and Ca values, moreover, do not entirely support the conversion absorption phenomena upon which the theory depends (83).

THE NATURE OF THE CALCIUM DEPOSIT. Analyses of calcification have revealed calcium, phosphorus, carbonate, magnesium, small traces of alkali salts and less constantly small amounts of iron (43) and of silica (105).

The calcium and phosphorus are present in relatively large amounts. Assuming that all magnesium is in the form of $Mg_3(PO_4)_2$ and all carbonate in the form of $CaCO_3$, it has been possible to speculate upon the composition of the probable compound formed by residual calcium and phosphorus and to consider the relative amounts of the various salts. By this calculation Howland, Marriott and Kramer (68) presented evidence that the ratio of residual calcium to residual phosphorus in freshly formed as well as in old bone was 1.94, the ratio necessary for the formation of tertiary phosphate, $Ca_3(PO_4)_2$. Kramer and Shear (88) (89) analyzed 11 specimens of normal bone and 7 of pathological calcification and found that all ratios averaged 1.96. They showed, however, that in three specimens taken from calcified fibromyomata of the uterus the ratios were 2.23, 2.23 and 2.18. Howland, Marriott and Kramer (68) found, moreover, in rachitic rats that the ratio of residual Ca to P was higher than in normal bones, showing 2.15 for the shafts, 2.10 for epiphyses and 2.38 for lines of freshly deposited lime salts. In spite of these variations, the close approach of the residual calcium phosphorus ratio to 1.94 has led to the belief that one of the solid phases in calcification must be tertiary calcium phosphate.

Analyses indicate that both calcium phosphate and calcium carbonate are present in all calcium deposits. Tanaka (151) found that a mixed precipitate was formed after injections either of calcium carbonate or calcium phosphate. Carbonate introduced into the peritoneal cavity after 2 to 5 days contained more phosphate than the usual pathological calcification. Pure calcium phosphate similarly injected contained on later analysis 10 per cent of calcium carbonate.

Estimations of the relative values of the two salts have been numerous. The analyses of Wells (167) in the calcified lymph nodes of bovine and human tuberculosis agreed closely with the older determinations of Zalesky and of Carnot for the composition of normal bone varying between 7.6 to 12.8 per cent for calcium carbonate and between 85.4 and 90.6 per cent for calcium phosphate.

Kramer and Shear (89), estimating the relationship of carbonate calcium to the total calcium, found values of 15 to 16 per cent in adult bone, of 8 to 10 per cent in young bones, and in a transitional series from 12 to 13 per cent. Carbonate calcium formed from 15 to 16 per cent of the total calcium in shafts, from 10 to 12 per cent in the new calcium deposit of rachitic bones studied by Howland, Marriott and Kramer. Goto (45) found much higher percentages of carbonate. The analyses of Wurm (172) are of great interest. In early calcification of tuberculous nodules, the composition of calcium salts corresponds to that of bones, the carbonate varying from 13 to 16 per cent. In late densely calcified apical lesions of tuberculosis, however, he found that calcium carbonate might constitute as much as 39 per cent of the total.

Many explanations have been offered for the co-existence of calcium phosphate and calcium carbonate in bone and pathological deposits. Kleinmann's contention that calcium phosphate removes calcium and carbonate from solution to form by conversion absorption calcium carbonate explains plausibly the constant presence of the two salts but with difficulty their varying proportions and the usual high ratios of phosphate (83).

The constant presence of the phosphate and carbonate in all calcifications and the approximate constancy of their relative amounts have frequently led to the assumption of a compound, a giant molecule in which the two salts are combined in definite proportion. Such a substance was hypothecated by Hoppe-Seyler (66) as long ago as 1877. Gassmann (41) attempted to explain the constancy of the proportion of calcium salts in bone by assuming that they exist in a definite compound with a closed ring which gave it great stability.

The question has recently been reopened by Taylor and Sheard (153) who have subjected calcium deposits to study by physical methods. They point out that $Ca_3(PO_4)_2$ has never been prepared in pure crystalline form in the laboratory, the product usually obtained being richer in calcium than could be accounted for by this formula. In the recognized forms of crystalline calcium phosphate, they find two, podolite $CaCO_3 \cdot 9\ CaO \cdot 3\ P_2O_5$ and dahlite $CaCO_3 \cdot 6\ CaO \cdot 2\ P_2O_5$ which contain

Ca and PO_4 in correct proportions for the hypothetical $Ca_3(PO_4)_2$. The actual determination of refractive indices and of x-ray diffraction patterns by Taylor and Sheard seem to indicate that the solid phase in bone is composed of minerals of the apatite series, 3 $Ca_3(PO_4)_2 \cdot Ca X_2$ with X_2 representing CO_3, F_2, $(OH)_2$, P or SO_4 and Ca which may to some extent be replaced by Mg. The experiments of Roseberry, Hastings and Morse (127), which were undertaken independently, indicate by x-ray spectrography that bone has a crystalline structure which is fundamentally that of other members of the apatite series of minerals. Chemical analysis by Bogert and Hastings (13) indicates that it exists in the form of a crystalline salt with the approximate formula of $CaCO_3 \cdot n\ Ca_3(PO_4)_2$ where n is not less than 2 nor greater than 3. They found no evidence that $CaHPO_4$ or $CaCO_3$ exists in bone as such. While the chemical nature of at least a portion of the deposits seems thus to be established, the different proportions of carbonate found by various observers and in various locations make it difficult to believe that the deposits are composed of a single substance.

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